THE ASSESSMENT OF PULMONARY HAEMODYNAMICS WITH MAGNETIC RESONANCE IMAGING IN PULMONARY HYPERTENSION

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Declaration

This thesis has been composed by Tarek Sami Saba and is the result of two years work and study at the Scottish Pulmonary Vascular Unit at the Western Infirmary, Glasgow, Scotland. The work on which this thesis is based is the candidates own although he was assisted and advised by members of the department of Radiology. This thesis has not been submitted in candidature for any other degree, diploma or qualification.

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Date 26/5/05

Abstract

Pulmonary hypertension is a rare disease characterised by high pulmonary vascular resistance. Prognosis depends upon mean pulmonary artery pressure at cardiac catheterisation. Historically, measurements of pulmonary haemodynamics and exercise capacity have been used to detect and monitor disease progression and treatment response, however these approaches have a number of limitations and deficiencies. We wondered whether an alternative strategy would be feasible; monitoring the adaptation response of the heart and pulmonary vasculature to pulmonary hypertension. Magnetic resonance imaging (MRI) is a new and exciting form of imaging with the potential to make accurate anatomical and physiological measurements in the cardiopulmonary circulation. In this thesis we set out to investigate whether anatomical and blood flow measurements made with MRI can detect and quantify raised pulmonary artery pressure at cardiac catheterisation. We then looked to see whether MRI has any advantages over doppler echocardiography, the current gold standard noninvasive investigation.

We enrolled twenty-eight subjects who were undergoing cardiac catheterisation and doppler echocardiography for investigation of suspected pulmonary hypertension at the Scottish Pulmonary Vascular Unit between September 1999 and March 2001. We used MRI to measure right and left ventricular mass, volume, and wall thickness, and aortic and pulmonary artery diameter. We calculated a novel ventricular mass index by dividing right ventricular mass by left ventricular mass. We then performed a flow quantification in the right pulmonary artery to measure mean and peak velocity of blood flow, acceleration time and ejection time, and calculated the ratio of acceleration time over ejection time. Finally we attempted to study the changes in these variables following straight leg raising exercise.

We found that our ventricular mass index ($r = 0.81$), right ventricular wall thickness ($r = 0.83$) and the ratio of main pulmonary artery over aortic diameter ($r = 0.82$) showed better agreement with mean pulmonary artery pressure than doppler echocardiography ($r = 0.77$) with sensitivity and specificity at least as good. We found significant correlations between right ventricular mass and end-diastolic volume with left ventricular mass ($r = 0.53$ and $r = 0.83$ respectively). This suggests either an association between pulmonary

hypertension and left ventricular hypertrophy or a survival advantage in those with more massive left ventricles, perhaps due to decreased ventricular compliance protecting left ventricular filling. Mean and peak velocity of blood flow in the right pulmonary artery were sensitive and specific markers of the presence of pulmonary hypertension, but not of severity. Contrary to the published literature, acceleration time and the ratio of acceleration time over ejection time did not correlate with pulmonary artery pressure. We were able to detect changes in all right pulmonary artery blood flow variables in a small number of subjects after exercise, but we encountered some practical difficulties and the significance of these observations is uncertain.

In summary, we have shown that anatomical measurements made in the cardiopulmonary circulation with MRI can be used to estimate pulmonary artery pressure with greater accuracy than doppler echocardiography. These estimates are likely to be more reliable than those provided by echocardiography, and may also give a measure of the recent burden of pulmonary vascular disease. An analogy may be made with the use of glycosylated haemoglobin instead of glucose in diabetes; pulmonary artery pressure fluctuates on a minute by minute basis whereas anatomical measurements reflect sustained changes in pulmonary haemodynamics. It should be said that this approach to the detection and monitoring of pulmonary hypertension has not yet been fully validated. Further work needs to be done to test whether it is sensitive to change in longitudinal follow-up and address the issue of inter and intraobserver reproducibility. Finally, we have also shown that MRI measurements of blood flow are sensitive and specific indicators of pulmonary hypertension, and that it may be possible to use MRI to study exercise-related changes in blood flow.

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Contents

List of figures and illustrations

Abbreviations

AOD	diameter of descending aorta
ASD	atrial septal defect
AT	acceleration time
Bo	external magnetic field
BSA	body surface area
CHD	congenital heart disease
cm/s	centimetres per second
CO	cardiac output
CTEPHT	chronic thromboembolic pulmonary hypertension
CTD	connective tissue disease
Echo	doppler echocardiography
ECG	electrocardiogram
ET	ejection time
g	grams
HHT	hereditary haemorrhagic telangiectasia
LVEDV	left ventricular end-diastolic volume
LVM	left ventricular mass
LVPWT	left ventricular posterior wall thickness
L/min	litres per minute
mm	millimetres
mmHg	millimetres of mercury
ms	milliseconds
MPAD	diameter of main pulmonary artery
MPAP	mean pulmonary artery pressure
MRI	magnetic resonance imaging
MV	mean velocity
NMV	net magnetisation vector
NS	not significant
PAHT	pulmonary hypertension

PAOP	pulmonary artery occlusion pressure
PASP	pulmonary artery systolic pressure at echocardiography
PP	portopulmonary hypertension
PPH	primary pulmonary hypertension
PV	peak velocity
PVR	pulmonary vascular resistance
RHC	right heart catheterisation
RVEDV	right ventricular end-diastolic volume
RVM	right ventricular mass
RVWT	right ventricular wall thickness
SD	standard deviation
T	tesla
TE	echo time
TR	repetition time
VMI	ventricular mass index
VSD	ventricular septal defect
6mwt	six minute walk test

Publications and presentations to learned societies

TS Saba, J Foster, M Cockburn, M Cowan and AJ Peacock. Ventricular mass index using magnetic resonance imaging accurately estimates pulmonary artery pressure. European Respiratory Journal 2002; 20: 1519 – 1524.

TS Saba, J Foster, M Cockburn, M Cowan and AJ Peacock. Assessment of pulmonary haemodynamics with magnetic resonance imaging. Scottish Thoracic Society meeting, June 2000 (Oral presentation).

TS Saba, J Foster, M Cockburn, M Cowan and AJ Peacock. Calculated ventricular mass index using magnetic resonance imaging accurately predicts mean pulmonary artery pressure in pulmonary hypertension. British Thoracic Society winter meeting, London, December 2000 (Oral presentation).

TS Saba, J Foster, M Cockburn, M Cowan and AJ Peacock. Role of magnetic resonance imaging in the evaluation of pulmonary hypertension. International Society of Magnetic Resonance Imaging meeting, Glasgow April 2001 (Poster).

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1 Introduction

1.1 Historical perspective: from the first to the third millenium

The first person to accurately describe the pulmonary circulation was Ibn An-Nafis, a physician who lived in Cairo in the 13th Century. He observed that the pulmonary artery carried blood from the right side of the heart to the lungs, where it was allowed to mix and combine with air in the alveoli before returning via the veins to the left side of the heart. The function of the pulmonary circulation as the source of oxygen uptake and carbon dioxide disposal was not worked out until the 17th and 18th centuries. Major differences in physiology and regulation between the systemic and pulmonary circulations, such as the response to hypoxia, were not recognised until much more recently with the advent of invasive haemodynamic monitoring. In the past two decades, doppler echocardiography has provided us with a useful means of making measurements in the pulmonary circulation non-invasively.

This is an exciting time to be a pulmonary vascular physician. Throughout the 20th century, established pulmonary vascular disease resulting in pulmonary hypertension has been regarded as untreatable and almost universally fatal. This therapeutic nihilism has meant that there has been a relative lack of interest in improving diagnostic techniques because there seemed to be little point in making the diagnosis since we could not alter the course of the disease. This began to change with the development of novel surgical approaches and the advent of continuous intravenous prostacyclin therapy, but this was only of benefit to a small number of patients. However, in the past few years there have been six randomised placebo-controlled studies of a range of new medical treatments, four with positive results. It has become obvious that we need a reliable and accurate non-invasive method of making measurements of pulmonary haemodynamics, a role that has only been partially fulfilled by doppler echocardiography. This has led to a resurgence in interest in diagnostic methods and was the stimulus for this thesis.

1.2 The healthy pulmonary circulation

1.2.1 Anatomy

1.2.1.1 The right ventricle

The normal right ventricle is an elliptical thin-walled structure wrapped around the more muscular and symmetrical left ventricle. This is a result of the much greater pressures generated by the left ventricle during systole which cause the interventricular septum to protrude into the right ventricular cavity. Similarly the left ventricular wall is about eight times as thick as the atrial walls, whereas the right ventricular free wall is only about three times as thick. The right atrium is situated at the base of the ventricle and forms the right margin of the heart. The right side of the heart receives its blood supply from the right coronary artery and the anterior interventricular branch of the left coronary artery. Blood drains into the right atrium via the superior and inferior vena cavae, enters the right ventricle through the tricuspid valve during diastole and is ejected during systole.

1.2.1.2 The pulmonary vasculature

Two distinct arterial and venous circulations serve the lungs. The main pulmonary artery arises from the base of the right ventricle and is approximately five centimetres long. It divides into the right and left pulmonary arteries which then divide many more times to form the pulmonary capillary bed. The right pulmonary artery is longer and straighter than the left, passing below the arch of the aorta into the right hemithorax. The function of the pulmonary arteries is to deliver deoxygenated blood from the right ventricle to the lungs for gas exchange to take place. Oxygenated blood then drains back into the left atrium by four pulmonary veins. At any one time, the blood volume of the lungs is approximately 450 ml, 70 ml of which is in the capillaries and the remainder shared between the arteries and veins.

The bronchial arteries arise from the descending aorta and its branches and therefore carry oxygenated blood. They carry about one to two percent of cardiac output and supply pulmonary tissues down to the level of the respiratory bronchiole. The bronchial veins drain into the left atrium via the pulmonary veins.

1.2.2 Physiology

1.2.2.1 Pulmonary artery pressure

The pressures at rest in the pulmonary circulation are shown in Table 1A with left sided pressures for comparison. These pressures can all be measured by catheterisation of the right and left circulation apart from left atrial pressure which can only be directly measured by percutaneous means. It can however be estimated from the capillary wedge pressure (section 1.4.3.1). Systolic pulmonary artery pressure can also be indirectly estimated by doppler echocardiography (section 1.4.3.2.1).

The lungs are unique in that they accommodate a blood flow equal to that of all the other organs in the body. The cardiac output of the right ventricle is essentially equal to that of the left. This coupled with the nine-fold difference in blood volume between the pulmonary and systemic circulations would be expected to result in a high pressure system were it not for the low compliance of the pulmonary circulation. The pulmonary arteries are all thin and distensible, and although relatively short, have much larger diameters than their counterparts in the systemic circulation. The wall thickness of the main pulmonary artery is only twice that of the venae cavae and a third that of the aorta. Furthermore, about half the blood volume ejected by the right ventricle is simultaneously emptied into the capillaries, veins and left atrium, thus preventing an even higher pulse pressure. The right ventricle cannot tolerate large acute rises in systolic pressure without failing, however pressures as high as those seen in the systemic circulation are sometimes seen in chronic disease.

Table 1A: Normal pressures in the cardiopulmonary circulation (mmHg)

	Mean	Systolic	Diastolic
Right atrium	2	-	-
Right ventricle	-	25	0
Pulmonary artery	15	25	9
Pulmonary capillary pressure	7	-	-
Pulmonary capillary wedge pressure	5	-	-
Left atrium	2-3		
Left ventricle	-	120	0
Aorta		120	80

1.2.2.2 Cardiac output

Cardiac output at rest is approximately 5L/min. It can be calculated as follows:

Cardiac output = Stroke volume x Heart rate

To account for variation in body size, it is often expressed as cardiac index as follows:

$$\text{Cardiac index} = \frac{\text{Cardiac output}}{\text{Body surface area}}$$

Giving an average cardiac index of approximately 3L/min/m^2. Cardiac output varies widely with activity level and can be difficult to measure accurately and reproducibly. It is usually measured with a pulmonary artery catheter but a number of non-invasive methods are available. Cardiac output is governed by the need to deliver an adequate supply of oxygen to the tissues and is therefore regulated by a number of factors, including the autonomic nervous system, local tissue metabolism and venous return, in accordance with the Frank-Starling law.

An alternative approach is to measure ejection fraction which is the percentage of ventricular volume at the end of diastole that is actually ejected during systole. This is normally estimated non-invasively using echocardiography but can be calculated by invasive means. Not all the blood leaving the right ventricle under resting conditions

enters the pulmonary circulation; it is possible to demonstrate a mild degree of physiological tricuspid regurgitation in a large proportion of normal people using echocardiography (1).

1.2.2.3 Resistance

Another useful measurement in clinical practice is resistance, which can be calculated using Ohm's law in two ways:

Total pulmonary resistance:

$$= \frac{\text{Mean pulmonary artery pressure (mmHg)}}{\text{Cardiac output (L/min)}}$$

Pulmonary vascular resistance:

$$= \frac{\text{(Mean pulmonary artery pressure – Pulmonary capillary wedge pressure) (mmHg)}}{\text{Cardiac output (L/min)}}$$

Total pulmonary resistance is a measure of the total resistance experienced by the right ventricle including the left heart, whereas pulmonary vascular resistance is a measure of the resistance due to the pulmonary circulation alone.

1.2.2.4 Physiological shunt

In normal individuals, blood in the aorta has a pO2 about 2 mmHg less than that of blood which has just equilibrated with alveolar air. This is because approximately 2% of blood leaving the left ventricle has bypassed the pulmonary capillaries and therefore not been oxygenated. This is mostly explained by the bronchial circulation draining into the left side of the heart, but there is further dilution of the oxygenated blood in the left ventricle

by blood that flows from the coronary arteries directly into the chambers of the left heart via the thebesian veins.

1.2.3 Homeostasis

Pulmonary haemodynamics are actively controlled by a number of factors which are not discussed in detail here. The endothelium produces several vasoactive factors including Nitric oxide, endothelins, prostaglandins, leukotrienes, thromboxane and platelet activating factor. The pulmonary circulation responds to hypoxia with vasoconstriction, unlike the systemic circulation (2). Neural and humoral factors are also involved, although they are thought to play a minor role. Cardiac output, gravity and lung volume provide passive control.

1.3 Pulmonary hypertension: an overview

1.3.1 Background

The pathological changes of pulmonary hypertension were first described by Romberg in 1891 (3) in a patient with unexplained pulmonary arteriosclerosis. In 1951, Dresdale et al coined the term primary pulmonary hypertension (4) and widespread awareness of the disease came with the epidemic of pulmonary hypertension, blamed on the use of the appetite suppressant aminorex fumarate, that swept Europe in 1967. It took almost 90 years for the first effective medical and surgical treatment to become available, but in the past ten years there have been dramatic improvements in both quality of life and survival with the use of calcium channel blockers and prostacyclin. This has led to increasing recognition of the important role that pulmonary vascular disease plays in many disease processes, and renewed interest in early diagnosis and intervention.

1.3.2 Definition and classification

Pulmonary hypertension (PAHT) has been defined as a mean pulmonary artery pressure of over 25 mmHg at rest or 30 mmHg during exercise at right heart catheterisation (5). It has traditionally been classified as either primary or secondary after clinical assessment (Table 1B), but the realisation that the underlying pathological abnormalities in some types of secondary disease were very similar to those seen in primary pulmonary hypertension prompted a new classification based upon histology (Table 1C). This was proposed at the second World Health Organisation symposium held in Evian, France in 1998 (6). To avoid confusion, the traditional classification will be used throughout this work unless otherwise indicated, since this has been used almost exclusively in the recent literature.

Table 1B: Traditional classification of pulmonary hypertension

Primary Pulmonary Hypertension
(including Familial disease)

Secondary Pulmonary Hypertension due to:

Connective Tissue Disease
- Scleroderma/CREST syndrome
- Mixed connective tissue disease
- Overlap syndrome
- Systemic lupus erythematosis

Chronic Hypoxic Lung Disease
- Chronic obstructive pulmonary disease
- Sleep disordered breathing
- Interstitial lung disease

Thromboembolic Disease
- Pulmonary thromboembolism
- In situ thrombosis
- Sickle cell disease

Congenital Heart Disease
- Venticular septal defect
- Atrial septal defect

Left-sided Heart Disease
- Valvular disease
- Left ventricular failure

Drugs
- Appetite suppressants
- Amphetamines
- L-tryptophan
- Cocaine

Portal Hypertension

HIV

Other
- Chronic high altitude
- Neonatal lung disease
- Pulmonary veno-occlusive disease
- Sarcoidosis
- Schistosomiasis

Table 1C: New WHO classification of pulmonary hypertension 1998

1. Pulmonary Arterial Hypertension
   - 1.1 Primary Pulmonary Hypertension
     - (a) Sporadic
     - (b) Familial
   - 1.2 Related to:
     - (a) Collagen Vascular Disease
     - (b) Congenital Systemic to Pulmonary Shunts
     - (c) Portal Hypertension
     - (d) HIV Infection
     - (e) Drugs / Toxins
       - (1) Anorexigens
       - (2) Other
     - (f) Persistent Pulmonary Hypertension of the Newborn
     - (g) Other
2. Pulmonary Venous Hypertension
   - 2.1 Left-Sided Atrial or Ventricular Heart Disease
   - 2.2 Left-Sided Valvular Heart Disease
   - 2.3 Extrinsic Compression of Central Pulmonary Veins
     - (a) Fibrosing Mediastinitis
     - (b) Adenopathy / Tumours
   - 2.4 Pulmonary Veno-Occlusive Disease
   - 2.5 Other
3. Pulmonary Hypertension Associated with Disorders of the Respiratory System and/or Hypoxaemia
   - 3.1 Chronic Obstructive Pulmonary Disease
   - 3.2 Interstitial Lung Disease
   - 3.3 Sleep Disordered Breathing
   - 3.4 Alveolar Hypoventilation Disorders
   - 3.5 Chronic Exposure to High Altitude
   - 3.6 Neonatal Lung Disease
   - 3.7 Alveolar-Capillary Dysplasia
   - 3.8 Other
4. Pulmonary Hypertension due to Chronic Thrombotic and/or Embolic Disease
   - 4.1 Thromboembolic Obstruction of Proximal Pulmonary Arteries
   - 4.2 Obstruction of Distal Pulmonary Arteries
     - (a) Pulmonary Embolism (thrombus, Tumour, OVA and/or parasites, Foreign Material)
     - (b) In-situ Thrombosis
     - (c) Sickle Cell Disease
5. Pulmonary Hypertension due to Disorders Directly Affecting the Pulmonary Vasculature
   - 5.1 Inflammatory
     - (a) Schistosomiasis
     - (b) Sarcoidosis
     - (c) Other
   - 5.2 Pulmonary Capillary Hemangiomatosis.

1.3.3 Histology

Three pathological patterns are seen in Primary Pulmonary Hypertension (PPH); plexogenic arteriopathy, thrombotic arteriopathy and veno-occlusive disease (7-9), although the latter has now been reclassified in the most recent WHO report (6). Plexogenic arteriopathy is characterised by the plexiform lesion, which consists of a mass of disorganised vessels associated with endothelial cells, smooth muscle cells and fibroblasts. It is also seen in secondary PAHT associated with collagen vascular disease, congenital heart disease and portopulmonary hypertension. In thrombotic arteriopathy there is evidence of old recanalised thrombus appearing as fibrous webs, thought to be due to either recurrent microembolism or in-situ thrombosis. In veno-occlusive disease there is widespread intimal proliferation of the intrapulmonary veins and venules, occasionally extending to the arteriolar bed.

1.3.4 Pathophysiology and natural history

As described earlier, the normal pulmonary circulation is a remarkably adaptable and compliant system, allowing for large variations in blood flow with relatively small changes in resistance and pulmonary artery pressure. This flexibility is gradually lost in the face of progressive vascular damage caused by a recurrent acute insult or an intrinsic disease process, and results in increased pulmonary vascular resistance. The right ventricle responds to this by hypertrophy, initially maintaining cardiac output and left ventricular filling pressure, albeit at the expense of a rise in pulmonary artery pressure which further damages the pulmonary endothelium. Right ventricular ischaemia may develop due to increased workload and insufficient coronary blood flow. Eventually the right ventricle begins to dilate and fail, mechanically compromising left ventricular function and leading to a fall in cardiac output. Death results from progressive right ventricular failure and arrhythmias.

1.3.5 Epidemiology

Primary pulmonary hypertension is a rare disorder, with an estimated incidence of one to two cases per million people per year. It is commoner in women (ratio 1.7:1) (5), perhaps due to a lower survival rate of male foetuses with the disease (10), and the mean age at the time of diagnosis is in the mid thirties. Untreated, the prognosis is bleak with a three year survival of 48% in one large series (11). The familial form of the disease probably accounts for 6% (5) and is indistinguishable clinically from the sporadic form (8). It is inherited in an autosomal dominant fashion with incomplete penetrance, and displays genetic anticipation (10). The causative gene has been mapped to chromosome 2q 31-32 (12) and has recently been identified as a mutation of the BMPR2 gene which codes for the type ll bone morphogenetic protein receptor (13, 14). At least 26% of sporadic cases display similar mutations (15).

The overall incidence of secondary pulmonary hypertension is unknown, but has been estimated at 0.5% to 53% depending upon the underlying disorder (Table 1D)(9, 16, 17). Little is known about prognosis in different types of secondary disease, although the outlook for connective tissue disease seems poor (16).

1.3.6 Treatment

1.3.6.1 Medical

Vasodilators are the mainstay of treatment for pulmonary hypertension. Calcium channel blockers are effective in a minority of patients who respond to an acute trial of vasodilators in the cardiac catheter laboratory – so called "responders" (18-22). Long term treatment with continuous intravenous prostacyclin improves exercise capacity and survival in both "responders" and "non-responders" (23-32). Treprostinil, a prostacyclin analogue given by continuous subcutaneous infusion (33, 34), nebulised iloprost (35), another prostacyclin analogue with a longer half-life and bosentan (36, 37), an endothelin antagonist have recently been shown to improve exercise capacity in placebo controlled

studies but their effect on survival is unknown. Uncontrolled studies have also reported short-term improvement in pulmonary haemodynamics with oral beraprost (38), oral sildenafil (39, 40) and inhaled nitric oxide gas (41). There is good evidence from post mortem and subgroup analyses that anticoagulation also improves survival (7, 20, 42).

Table 1D: Estimated prevalence of secondary pulmonary hypertension

Disease/condition	Prevalence
Connective tissue diseases overall	10%
CREST syndrome	< 50%
Mixed connective tissue disease	23 – 53%
Scleroderma	2.3 – 35%
Systemic lupus erythematosus	0.5 – 14%
Rheumatoid arthritis/Sjogrens syndrome/Dermatomyositis	Rare
Chronic obstructive pulmonary disease	Unknown
Fibrosing lung disease	Unknown
Portal hypertension	? 0.5 – 2%
HIV infection	? 0.5 – 2%
Use of anorectic agents	? 25 – 50 per million

1.3.6.2 Surgical

Transplantation is the most established of the three surgical options currently available for this disease. The first successful heart-lung transplantation was performed in a patient with primary pulmonary hypertension (43). Operative mortality ranges from 16-29% depending upon aetiology with one, three and five year survival between 70-75%,, 55-60% and 40-45% respectively (6). The timing of referral to a transplant centre remains a difficult issue, especially in the light of recent advances in medical therapy.

Atrial septostomy was first performed by Rich and Lam in 1983 (44), and since then several investigators have reported a beneficial effect on pulmonary haemodynamics

(45-48). The rationale is to artificially create a right to left shunt thereby increasing cardiac output and systemic oxygen delivery, and reducing right atrial pressure. Unresolved issues include mechanism of action, optimal timing of intervention, choice of technique (blade balloon or graded balloon dilation), and long term effects (49).

Pulmonary thromboenderarterectomy is very effective in carefully selected patients with proximal thromboembolic disease demonstrated at angiography. Surgery results in an increase in pulmonary blood flow and cardiac output, extended survival, and improved quality of life (50).

1.4 Monitoring the pulmonary circulation

1.4.1 The importance of monitoring

The pulmonary circulation is frequently involved in systemic and cardiorespiratory disease. Bedside clinical assessment is a poor measure of disease severity (51), and an objective assessment of the cardiopulmonary circulation is often required to monitor disease progression and the response to treatment. Ideally these measurements would be noninvasive and allow us to predict mortality and guide the timing of surgical referral. This has become increasingly important with the advent of effective therapy, since pulmonary hypertension is now considered a treatable disease. The development of novel medical and surgical approaches to treatment means that we need a method of making regular reliable objective measurements of the burden of disease, both for clinical trails of these new therapies and for clinical practice.

1.4.2 Which endpoints should we measure?

The traditional approach has been to measure pulmonary haemodynamics, namely pulmonary artery pressure, cardiac output and resistance. We know that reliable and reproducible measurements can be made invasively during cardiac catheterisation. This has been further refined with the use of ambulatory pulmonary artery pressure monitoring which has revealed significant postural and diurnal variation (52). These measurements have been shown to give useful prognostic information (11), but the timing of surgery, in particular transplantation, remains difficult. In any case, cardiac catheterisation is invasive, potentially hazardous, and requires hospital admission, and is therefore unsuitable for frequently repeated measurements.

Unfortunately there is no simple sphygmomanometer for the pulmonary circulation and accurate reproducible non-invasive measurements have been difficult to make. The most widely used method at present is doppler echocardiography, but this has a number of limitations that will be discussed later.

An alternative approach, adopted by many of the recent trials of new therapies, has been to measure exercise tolerance. This has been done by means of the six minute walk test, the shuttle walk test and cardiopulmonary exercise testing.

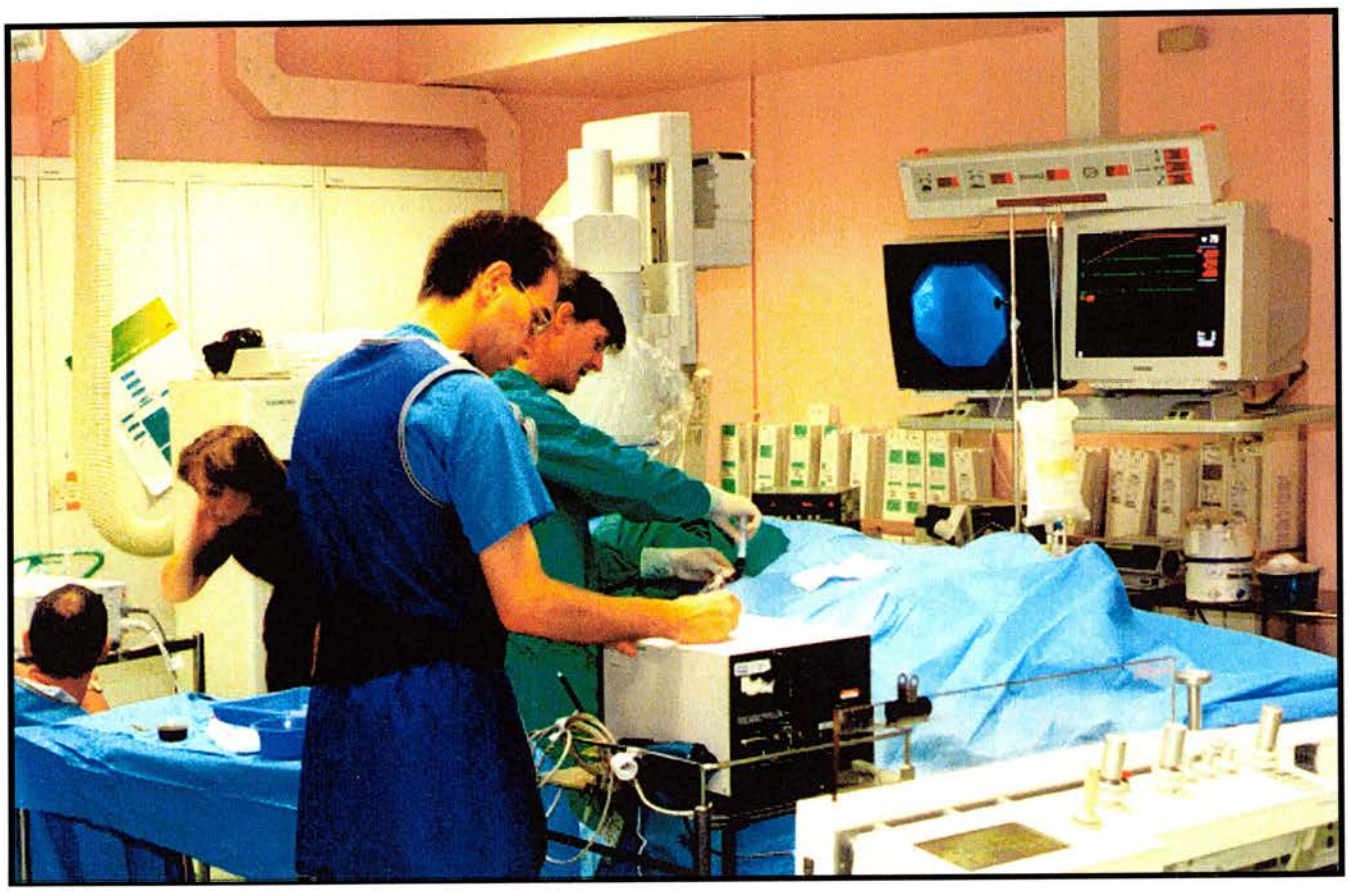
1.4.3 Measuring pulmonary haemodynamics

1.4.3.1 Right heart catheterisation

1.4.3.1.1 Pulmonary artery pressure

The definitive method of assessing pulmonary haemodynamics is right heart catheterisation, first performed by Lewis Dexter in 1945 (53). This is done by passing a pulmonary artery catheter into the great veins via an internal jugular, subclavian, femoral or brachial approach, and guiding it into the right atrium, ventricle and pulmonary arteries under fluoroscopic guidance. Dexter showed that this technique could be used to measure pressure and oxygen saturation in the great veins and right heart chambers as well as in the pulmonary artery. He later showed that an estimate of left atrial filling pressure, the "wedge pressure", could be obtained by transiently occluding a distal branch of the pulmonary artery, assuming the presence of an uninterrupted column of blood between catheter tip and left atrium (54). The technique was refined in 1970 by Swan et al with the introduction of the balloon tipped catheter (55), which could be inserted at the bedside without the need for fluoroscopy. Right heart catheterisation, usually performed in a cardiac catheter laboratory (Figure 1A), is now a routine procedure at specialist units, but it is not without its risks. There is significant morbidity and the incidence of life-threatening complications is approximately 0.5-1% in this patient group (42, 56, 57), rising to 2-4% if pulmonary angiography is also performed (58, 59).

Figure 1A: Cardiac catheter laboratory



1.4.3.1.2 Cardiac output

There are principally two methods by which cardiac output can be measured with a cardiac catheter, the direct Fick method and the indicator dilution method.

Fick method

The Fick principle states that the amount of a substance taken up by an organ must be equal to the arterial concentration minus the venous concentration multiplied by the blood flow. This can be applied to the uptake of oxygen by the lungs as follows:

Volume of O2 taken up (VO2 ml/min)

$$= \frac{\text{Arterial O2 concentration (paO2 ml/L)} - \text{Venous O2 concentration (pvO2 ml/L)}}{\text{Cardiac output (CO L/min)}}$$

Or:

$$\text{CO (L/min)} = \frac{\text{paO2 (ml/L)} - \text{pvO2(ml/L)}}{\text{VO2 (ml/min)}}$$

A sample of venous blood is taken, preferably from the pulmonary artery to minimise the risk of incomplete mixing and the effect of left to right shunts. Blood is also taken from a peripheral systemic artery, while oxygen uptake is simultaneously determined by means of a metabolic cart or reservoir bag technique. The method is accurate but clearly time consuming and invasive. It has become the method of choice in determining CO in the presence of shunting, such as in congenital heart disease.

Indicator dilution method

In the indicator dilution technique, a known quantity of indictor is injected into a large vein or preferably into the right heart or pulmonary artery itself. Repeated samples of

peripheral systemic arterial blood are taken and the concentration of indicator plotted on a graph against time. The initial decline in concentration is extrapolated to the x-axis to give the time taken for the entire bolus of indicator to pass the arterial sampling point, and the mean indicator concentration during that time period is then calculated. Total CO in litres for that time period is then equal to the amount of indicator injected divided by its mean arterial concentration, and CO in litres per minute can then be calculated. The method is limited by the need for a non-toxic indicator that remains in the blood stream and does not accumulate in body tissues during repeated measurements, such as indocyanine green.

Thermodilution

A refinement of indicator dilution is the technique of thermodilution, which was first described by Fegler et al in 1954 (60). A number of subsequent animal studies demonstrated its practicality and reliability (61, 62), however it was not used in human subjects until Ganz et al showed in 1971 that it was much simpler than indicator-dye dilution with similar accuracy and reproducibility (63). The balloon-tipped pulmonary artery catheter became commercially available shortly afterwards and became the method of choice (55). Invasive measurements of pulmonary haemodynamics with an indwelling catheter are now routinely made in the care of critically ill patients and used to guide management and predict prognosis. The benefits of this approach seemed obvious to clinicians and were never subjected to objective assessment. Recently however there has been increasing evidence of significant associated mortality and morbidity in the acute setting (64) and there have been growing calls for a moratorium on their use until an adequate randomised controlled trial has been undertaken.

1.4.3.2 Doppler echocardiography

1.4.3.2.1 Pulmonary artery pressure

Three methods of assessing pulmonary artery pressure have been described using doppler echocardiography (Figure 1B): continuous wave doppler of the tricuspid valve, pulsed wave doppler of the pulmonary outflow tract and right ventricular isovolumic relaxation time.

Continous wave doppler

In 1984 Yock and Pop described a method of assessing pulmonary artery pressure using doppler echocardiography (65). They pointed out that pulmonary artery systolic pressure was the same as right ventricular systolic pressure in the absence of a pressure gradient across the pulmonary valve. They then showed that right ventricular systolic pressure could be calculated if right atrial pressure and the maximum velocity of tricuspid regurgitation were known using a modified form of the Bernouilli equation as follows:

Right ventricular to right atrial pressure gradient

$$= 4 \times (\textit{maximum velocity of tricuspid regurgitation jet})^2$$

This shows that the velocity of tricuspid regurgitation depends only upon the pressure difference between the right ventricle and the right atrium, and not on the geometry of the valvular orifice. They then measured tricuspid regurgitation by positioning a doppler ultrasound beam in line with blood flow through the valve, using continuous wave recordings to determine peak velocity, and estimated right atrial pressure by measuring central venous pressure (Figure 1C). Conventional echocardiography can then be used to exclude the presence of a gradient across the pulmonary valve. They applied this method in a study of 62 patients with clinical signs of right heart failure. Tricuspid regurgitant

Figure 1B: Doppler echocardiography

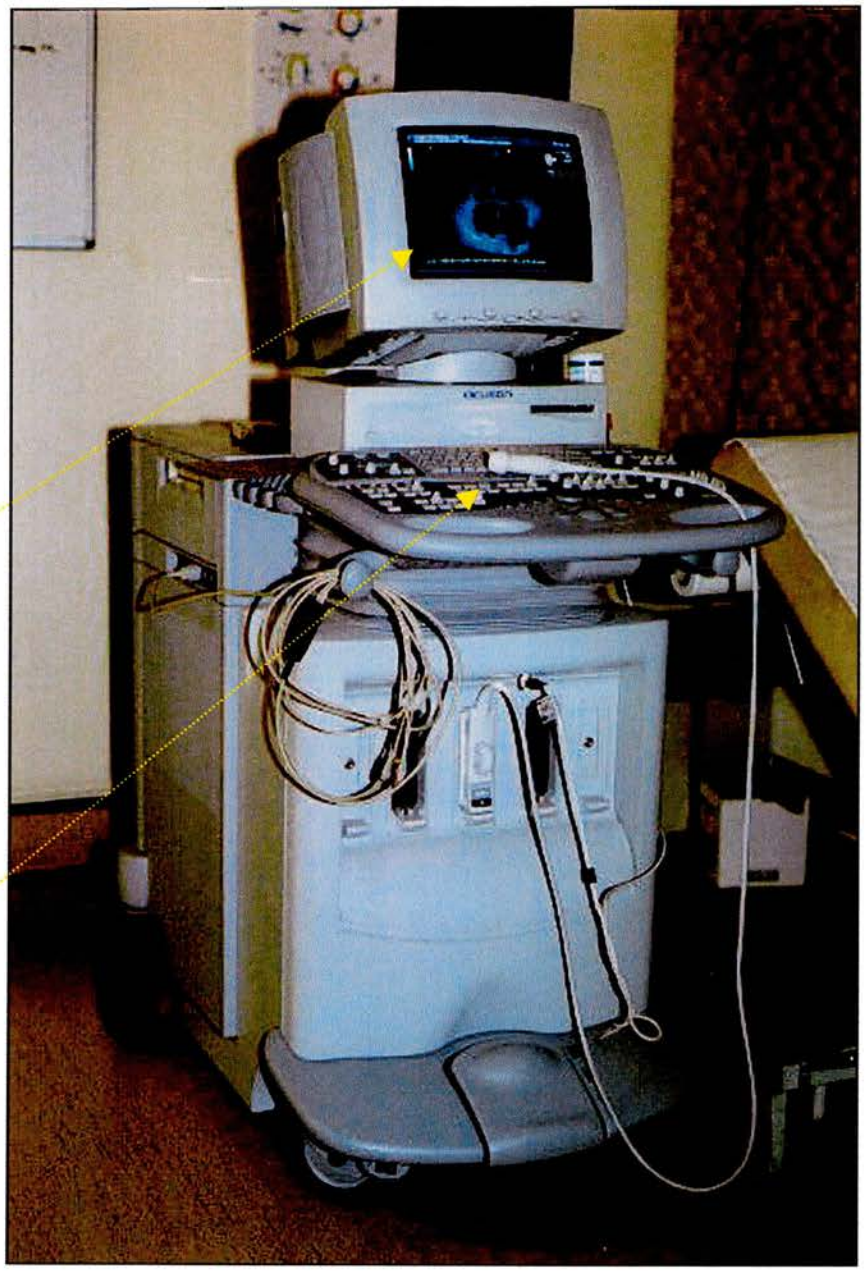
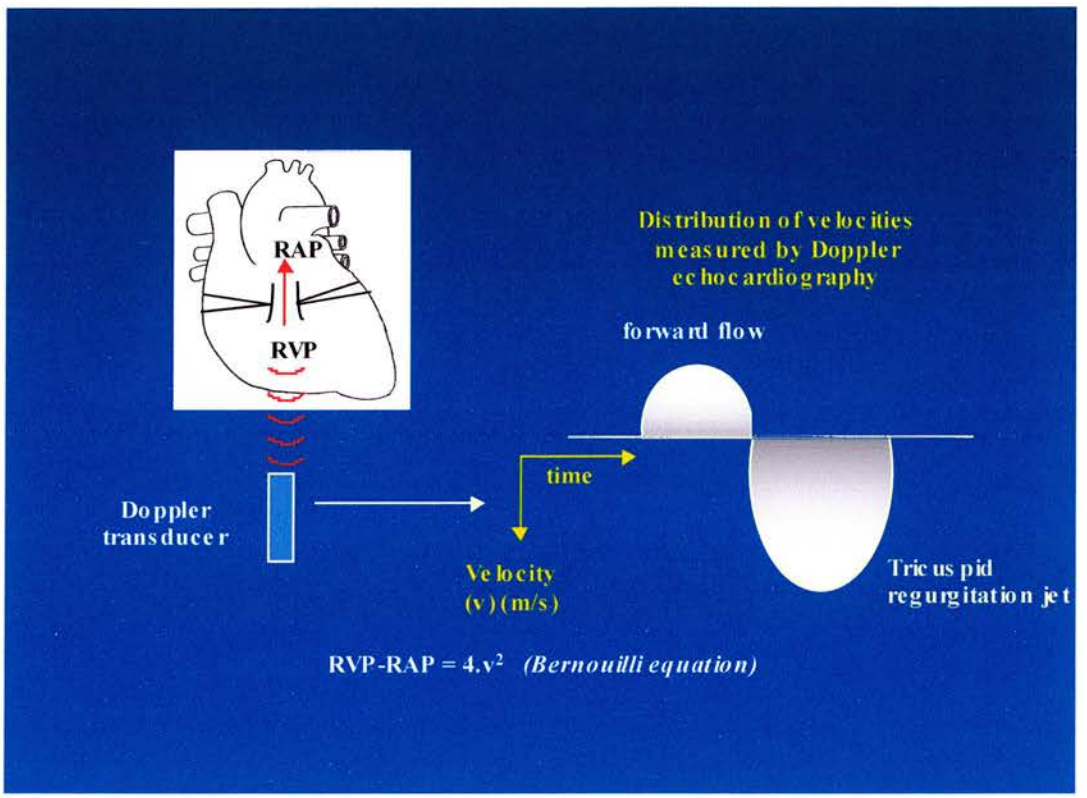


Figure 1C: **Estimation of systolic pulmonary artery pressure from tricuspid regurgitation jet using doppler echocardiography**



RAP = right atrial pressure, RVP = right ventricular pressure

jets were clearly recorded in 87% of subjects and right atrial pressure was estimated clinically from the jugular veins. They reported very close agreement with catheter measurements (r = 0.93, standard error 8mmHg) although these were not made simultaneously (65).

A number of studies have reported correlation coefficients of between 0.89 and 0.87 with cardiac catheterisation in subjects with pulmonary hypertension due to primary disease, connective tissue disease, congenital heart disease and left heart disease (65-69). Interobserver variability appears to be less than 3% and measurements are unaffected by cardiac output (66) Measurements seem to be accurate over a range of pressures (65-69), however the correlation coefficients do not tell the whole story and can be misleading (70). The standard error reported in these studies ranges from 5-9 mmHg in comparison to catheter measurements and both false negative (71) and false positive (69, 72, 73) measurements have been reported. This difference can be explained in a number of ways. Catheter and doppler measurements were not made simultaneously in most studies. There is often uncertainty in measuring the maximum velocity of the tricuspid regurgitant jet and an unavoidable angle between the jet and the hand held doppler probe (65). The maximum pressure difference across the tricuspid valve may occur before peak right ventricular pressure in some situations (65). Furthermore, the frequency response of fluid-filled pulmonary artery catheters may be too slow for instantaneous measurements to be made (74). There is also evidence from high fidelity transducer tipped catheter studies that the assumptions made about the orifice geometry of the tricuspid valve in the Bernoulli equation are incorrect (71).

A further source of error is the value assigned to right atrial pressure. Yock and Pop reported only a modest correlation between clinical assessment and invasive measurement (65). Some authors have used a fixed value ranging between 5 mmHg (75) and 14 mmHg (68) while others have proposed using the response of the inferior vena cava to inspiration as a guide (76, 77). Chan et al found that a fixed value of 14 mmHg gave more accurate results than an estimated pressure (68). Others have not found it necessary to take right atrial pressure into account to get accurate results (67). This variation in method makes it difficult to compare the results of different studies.

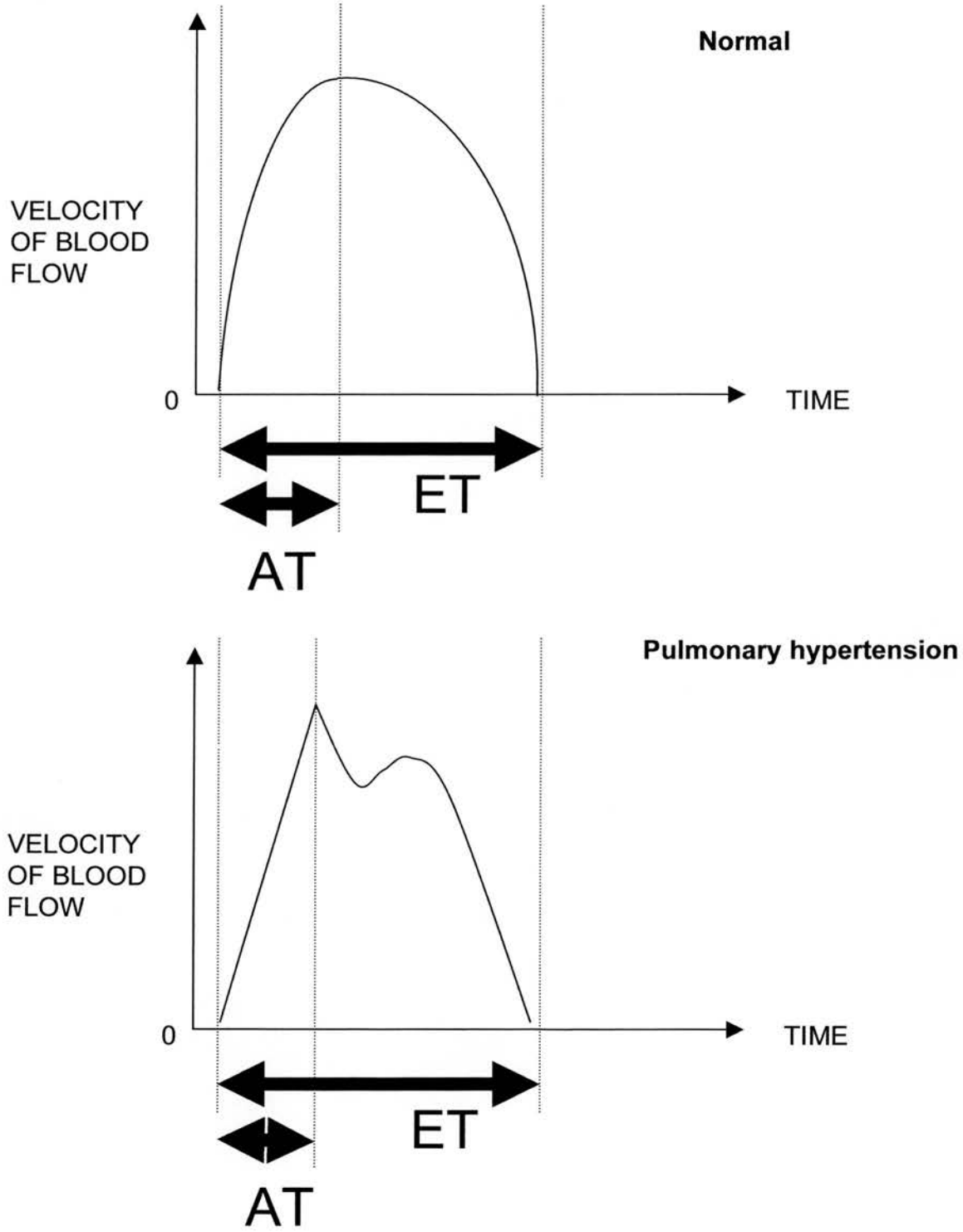
Tricuspid regurgitation can be detected in approximately 50% of normal subjects (1) and almost all those with clinical signs of right heart failure (65, 66), especially in the presence of a systolic pulmonary artery pressure of more than 50 mmHg (66, 67). However success rates are lower in the absence of clinical right heart failure (68) and measurements are not possible in a significant proportion of subjects. Denton et al reported a failure rate of 39% in subjects with systemic sclerosis due to absence of suitable tricuspid regurgitation (69). Currie et al found analysable tricuspid regurgitant jets in only 80% of subjects with raised pulmonary artery pressure (66). Chronic obstructive pulmonary disease is a particular problem with success rates of only 24 - 66% in some studies (75, 78) although this can be improved by means of saline contrast enhancement (76).

Pulsed wave doppler

In 1983, Kitabatake et al used a pulsed doppler technique to study pulmonary artery flow velocity in a series of 33 subjects, 16 of whom had a mean pulmonary artery pressure of more than 20 mmHg (79). They measured Acceleration time (AT) defined as the time in milliseconds between the onset of blood flow through the pulmonary valve and the maximum velocity of blood flow attained in the pulmonary outflow tract, and Ejection time (ET), the time between the onset and the end of blood flow through the pulmonary valve during a cardiac contraction (Figure 1D). They found that those with raised pressure had a shorter AT and that both AT and the ratio of AT/ET correlated well with mean pulmonary artery pressure ($r = 0.88$ and 0.9 respectively). In ten of the pulmonary hypertensive subjects a secondary slower rise was observed, resulting in mid-systolic notching of the flow velocity contour. Adequate measurements were obtained in 70% of subjects and 90% of those with raised pressure.

Subsequent studies have confirmed the sensitivity and low failure rate of this technique, but not all have shown similar accuracy. Isobe et al reported sensitivity and specificity of 93% and 97% respectively with good accuracy irrespective of cardiac output (80). On the other hand, Dabestani et al reported intraobserver and interobserver variability of 7% and 9% respectively and sensitivity and specificity of 78% and 100% respectively for AT, but

Figure 1D: **Measurement of acceleration time (AT) and ejection time (ET) at the pulmonary outflow tract**



a standard error of the estimate of 8.3mmHg with a correlation of 0.87 (81). Other studies have reported similar results in studies of primary pulmonary hypertension, chronic obstructive airways disease, congenital heart disease, left heart disease and connective tissue disease, with correlations with catheter measurements of between 0.7 and 0.88 for AT and AT/ET with mean pulmonary artery pressure or its logarithm and higher standard errors in some cases (82-86). Unlike doppler of the tricuspid regurgitant jet, the success of this method does not seem to depend upon disease severity and is not diminished in chronic obstructive airways disease (84, 86). In summary, pulsed doppler echocardiography appears to be a sensitive way of detecting the presence of pulmonary hypertension but does not consistently allow the accurate quantification of pulmonary artery pressure (87).

Isovolumic relaxation time

In 1967, Burstin et al described a method of indirectly estimating systolic pulmonary artery pressure from external graphic recordings (88). Using a jugular phlebogram to determine tricuspid valve opening and a phonocardiogram to determine pulmonary valve closure, he measured the isovolumic relaxation time of the right ventricle, defined as the interval between pulmonary valve closure and tricuspid valve opening. He was then able to predict peak pulmonary artery pressure by means of a nomogram that took account of heart rate. Hatle et al modified this techique in 1981, by using continuous wave doppler to study flow velocity wave forms in the tricuspid and pulmonary valves using cessation of flow in the latter and initiation of flow in the former to measure isovolumic relaxation time, and consequently pressure using Burstin's nomogram (89). Stevenson et al applied this technique in a study of 95 infants and children and reported a correlation coefficient of 0.86 unsedated and 0.96 sedated in comparison with cardiac catheterisation (90). A heart rate of more than 155 beats/min was associated with reduced accuracy. In a recent study, Caso et al were able to distinguish normal subjects, subjects with chronic obstructive lung disease and subjects with chronic obstructive lung disease and pulmonary hypertension (91).

Which method is best?

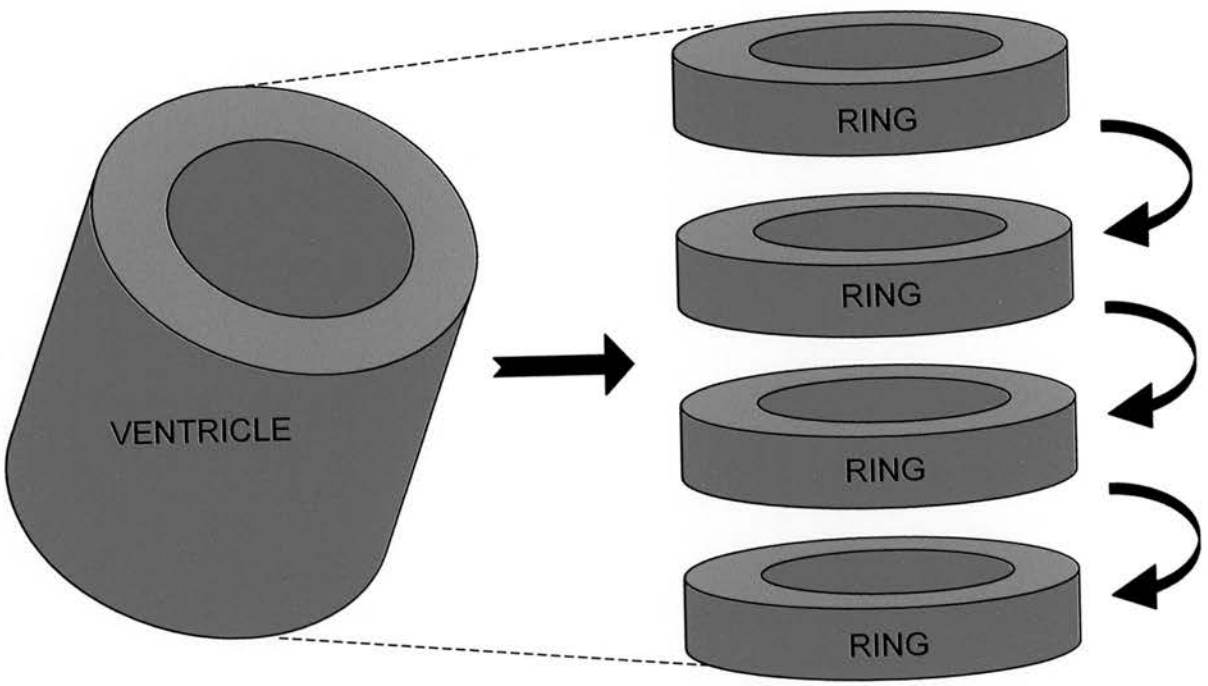
A number of studies have compared the accuracy of these methods (68, 78, 92). Chan et al studied fifty patients with a variety of conditions including primary pulmonary hypertension, cardiac valve disease and congenital heart disease (68). They reported a success rate of 72%, 88% and 22% using continuous wave doppler, pulsed wave doppler (AT) and isovolumic relaxation time respectively. Overall accuracy was better for continuous wave doppler ($r = 0.89$) than pulsed wave doppler ($r = 0.65$), but the latter improved in accuracy when only patients with a heart rate of between 60 and 100 beats/min were included (0.85). The low success rate using isovolumic relaxation time was due to the high incidence of arrhythmia. Torbicki et al performed a similar study in 72 patients with chronic lung disease (78). Continuous wave doppler was successful in only 17 patients with a correlation coefficient of 0.92. AT measured by pulsed doppler was successful in 68 out of 72 with a correlation coefficient of 0.72, a standard error of 8.3 mmHg and a positive predictive value for pulmonary hypertension of 84%. Isovolumic relaxation time succeeded in 59 out of 72 subjects with a correlation of 0.69 and a standard error of 12.3 mmHg. Chow et al found that continuous wave doppler predicted the change in pressure more reliably than pulsed wave doppler after pulmonary thromboendarterectomy (92).

No single doppler method provides accurate measurements in all patients. Chan et al showed that in 96% of patients at least one method was feasible (68). Continuous wave doppler appears to be the most useful and practical method because it allows more accurate quantification of pressure than pulsed wave doppler, and does not require a nomogram. It has now become the gold standard non-invasive method of assessing pulmonary artery pressure, and has made the screening of small numbers of "at risk" patients possible.

1.4.3.2.2 Cardiac output

Echocardiography can be used to measure stroke volume using Simpsons rule (Figure 1E). The ventricle is taken to be a cylinder and divided up into rings of the same

Figure 1E: **Calculation of stroke volume using Simpson's rule**



Volume of ventricle = Sum of volume of holes in 'rings'

Stroke volume = End-Diastolic volume - End-Systolic volume

thickness. The area of the "hole" in the ring is multiplied by the thickness to get the volume. The volume of all the holes in the rings is then added up to give an estimate of ventricular volume. This process is done in end-systole and end-diastole, and the former subtracted from the latter to obtain stroke volume. This is then multiplied by heart rate to obtain cardiac output. This requires considerable technical expertise and is often inaccurate due to left ventricular asymmetry because a two dimensional view of the left ventricle is extrapolated to derive three dimensional volumes. In addition measurements are difficult to obtain and standardise with changes in posture and physical activity.

A wide range of echocardiographic approaches have been described for the measurement of cardiac output using Doppler echocardiography, mostly in an Intensive or Coronary Care setting, using different cardiac locations and time-velocity integral measurements. Transoesophageal and transtracheal approaches have also been developed which have increased accuracy and reproducibility and several studies have shown a favourable comparison with thermodilution (93-97). In general Doppler echocardiography appears to be a useful method of monitoring trends in cardiac output in a controlled setting, but varying posture and inter-observer variability limit its accuracy for outpatient use. There is a need for an accurate, reproducible and minimally invasive method of assessing cardiac output.

1.4.4 Measuring exercise tolerance

1.4.4.1 Six minute walk test

Simple tests of exercise tolerance, of which this is the most widely used, are a useful way of detecting and monitoring changes in functional capacity due to cardiorespiratory disease and have the advantage of relating directly to the symptoms experienced by patients. The six minute walk test is very simple, requires inexpensive and easily available equipment, and is reproducible. It is a submaximal exercise test whereby the patient is asked to walk at a comfortable pace for six minutes along a measured course, usually with simultaneous pulse oximetry. The distance walked is recorded as well as the

heart rate and the degree of desaturation. The test is considered to be safe because it is self-limited and reflects the demands of everyday living (11, 98).

Performance in the six minute walk predicts survival in left ventricular dysfunction and advanced heart failure (99, 100). In 1996 Barst et al reported similar findings in 81 patients with primary pulmonary hypertension with NYHA III or IV and suggested that this test could be used to monitor individual patients (27). Miyamoto et al confirmed this finding, but only found weak correlations between distance travelled and cardiac output and total pulmonary resistance, and no correlation with mean pulmonary artery pressure (101). Longterm treatment with vasodilators improves performance during the six minute walk (27, 34, 36, 37), sometimes with minimal improvement in pulmonary haemodynamics (34).

Limitations of this form of monitoring are that results are easily influenced by the level of encouragement given by the tester, and by the cooperation and motivation of the patient. There is a also a clear learning curve, with some investigators incorporating one or more "Practice walks" into the study protocol to overcome this (34). Furthermore, the prognostic value of the six minute walk test has not been clearly established in subjects with NYHA I or II, or in those with secondary pulmonary hypertension, many of whom have significant comorbidity such as arthritis.

1.4.4.2 Cardiopulmonary exercise testing

Exercise testing with simultaneous gas exchange, electrocardiogram (ECG) and blood pressure measurements only became a practical process with the recent development of computers able to assimilate the large amount of data generated. Modern systems are able to calculate and display gas exchange data "live" during exercise, enabling the tester to continuously assess the adequacy of work rate and making the process safer for the patient.

There are a number of characteristic abnormalities seen in pulmonary hypertension, including decreased oxygen uptake and oxygen pulse and increased ventilatory equivalents (102), but it remains unclear whether any of these indices predict mortality. Rhodes et al showed that exercise capacity displays a close negative correlation with

right atrial pressure (57) which is itself a marker of poor prognosis (5), and that poor exercise capacity predicted mortality at cardiac catheterisation (57). Similarly, there is little published evidence showing that gas variables derived at cardiopulmonary exercise testing correlate with resting pulmonary haemodynamics, although there is evidence that pulmonary artery pressure on exercise correlates with ventilatory equivalents (103, 104). Thus although some authors have advocated serial exercise testing to monitor this group of patients (105, 106), more work needs to be done in this area.

1.4.5 Deficiencies of conventional investigation

Pulmonary hypertension is defined as an abnormality of pulmonary haemodynamics (6), and it is logical to attempt to monitor disease progression and treatment efficacy in terms of deterioration or improvement in these indices. This approach appears to be validated by the prognostic information derived from haemodynamic measurements, in particular right atrial pressure, mean pulmonary artery pressure and cardiac index (11).

The most widely used non-invasive technique, Doppler Echocardiography (65), is safe and widely available, but has several limitations as discussed earlier. It cannot measure *mean* pulmonary artery pressure and only provides an estimate of *systolic* pressure. It depends upon the presence of detectable tricuspid regurgitation and has a significant failure rate in some patient groups (78). Furthermore, measurements are somewhat operator-dependant, and influenced by physiological variables such as heart rate, hydration status and posture (52).

Fluid-filled pulmonary artery catheters have remained the gold standard method of measuring pulmonary artery pressure both for research and for clinical purposes, but are invasive and also have a number of limitations. The need for leveling an external pressure transducer with the catheter tip in the right atrium for calibration makes measurements during exercise and changes in posture difficult. Pressure measurements are not "real-time" and the signal may be damped by the fluid-filled lumen (107). Some authors have also expressed doubts about the relevance of measurements made in unrepresentative surroundings, arguing that they bear little relation to the pulmonary haemodynamic variation encountered by patients with everyday activity (107), a criticism that can also

be leveled at echocardiography. There is significant spontaneous variability in pulmonary artery pressure at rest (108). Rich et al made measurements of pulmonary haemodynamics hourly for six hours in twelve subjects with primary pulmonary hypertension, demonstrating average variability of 8% in mean pulmonary artery pressure and 13% in total pulmonary resistance (108). We also know from ambulatory micromanometer-tipped catheter studies that pulmonary artery pressure varies widely over the course of a twenty-four hour period (52, 103, 109), so it seems unlikely that these one-off measurements will provide a clinically relevant assessment of pulmonary haemodynamics. Ambulatory studies have demonstrated a similar phenomenon in the systemic circulation and guidelines now emphasize the importance of multiple measurements before anti-hypertensive treatment is initiated or modified. Similarly we know that cardiac output is a very labile measurement and it is a testament to the flexibility of the pulmonary circulation that this does not seem to translate into labile pulmonary artery pressure measurements.

There are a number of other criticisms that can be directed at a purely "haemodynamic" approach to monitoring these patients. The main symptom of patients with pulmonary hypertension is exercise intolerance, and this seems to correlate poorly with the degree of haemodynamic disturbance (101). This suggests the problem is not simply the severity of pulmonary hypertension but also the way that the heart and pulmonary circulation adapt or respond to it. This idea is supported by the finding of Raeside et al that pulmonary artery pressure correlates with ventilatory equivalents when both are measured during exercise, but that resting pulmonary haemodynamics do not seem to predict exercise haemodynamics (103). Furthermore, we do not know why some patients maintain cardiac function while others develop right heart failure in response to similar resting pulmonary haemodynamics; this also suggests a difference in response of the right ventricle.

Similarly, although exercise capacity appears to predict prognosis, this is only at the extremes of the scale, and correlation with prognosis is poor for the majority of patients (57). Miyamoto et al found that performance at six minute walk test predicted mortality in those patients who walked less than 332 metres, but did not report a direct correlation between distance walked and survival (101).

There is already evidence that genetic factors play a part in the adaptation responses of the right ventricle and pulmonary circulation. A mutation of the BMPR2 gene has been identified as the causative gene for familial and some sporadic pulmonary hypertension, however penetrance is incomplete suggesting a role for other factors (12-15). Deletion polymorphisms in the Angiotensin Converting Enzyme gene are associated with right ventricular hypertrophy, exercise induced pulmonary hypertension and tissue oxygenation in chronic obstructive airways disease (110-112). They are also associated with left ventricular hypertrophy and coronary artery disease (113-115), and the ability of elite mountaineers to climb above 7000 metres (116).

1.5 Magnetic resonance imaging

1.5.1 History

The phenomenon underlying MRI was first noticed by Rabi in 1939 who used it to probe particle beams. His techniques were later refined by Broch and Purcell in the 1940s and used to analyse the structures of solids and liquids. The first images of the live human body were obtained by Damadian et al in 1977 (117). Clinicians have not been slow to realise the implications for medical practice of a form of imaging capable of providing superb soft tissue resolution and accurate physiological information, all without the risk associated with X-ray exposure. Over the past two decades two-dimensional, three dimensional and functional imaging have become possible, and MRI has revolutionised imaging in cardiology and neurology in particular. As the technology has become less expensive and cumbersome it has become more widely available, but at the time of writing still remains the preserve of larger hospitals.

1.5.2 Theory: how does it work?

1.5.2.1 The atomic nucleus

MRI depends upon the ability of the atomic nucleus to absorb and emit energy, and the consequent variations in its behaviour in response to an externally applied magnetic field. Atoms are essentially made up of three components; protons and neutrons, which make up the nucleus, and electrons which orbit the nucleus. There are three forms of motion within the atom:

1) Spin of the nucleus on its axis
2) Spin of the electrons around their own axes
3) Orbit of electrons around the nucleus

Nuclear spin of atoms present in tissue provides the basis for MRI. Atomic nuclei with an odd mass number (sum of protons and neutrons) are "MR active". This is because the laws of electromagnetic induction state that spinning nuclei with a net charge induce a magnetic field around them, a "magnetic moment", with a North and a South pole. This magnetic moment has vector properties and means that the nuclei can be lined up with a strong external magnetic field.
A number of "MR active" nuclei are present in biological tissue, including:

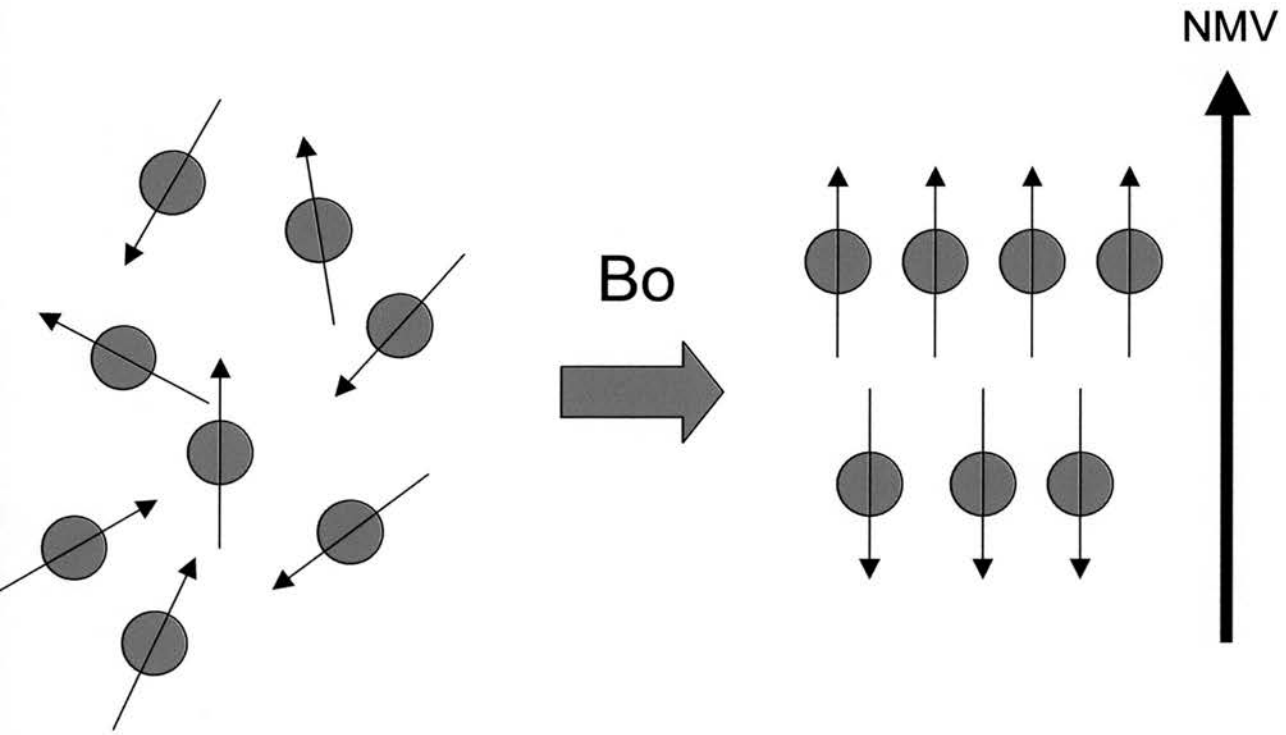
	Mass number
Hydrogen	1
Carbon	13
Nitrogen	15
Oxygen	17
Sodium	23

In clinical MRI the Hydrogen nucleus is used, because its small size gives it a relatively large magnetic moment, and it is widely present in the human body. The magnetic moment of Hydrogen is called the Net Magnetisation Vector (NMV).

1.5.2.2 The external magnetic field (Bo)

The unit of magnetic field strength is the Tesla (T). Fields in clinical use currently range between 0.3 T and 2 T. Hydrogen nuclei in biological tissue are usually randomly aligned. When a powerful magnetic field is applied to the human body, they respond by lining up either parallel (low energy or "spin up" nuclei) or antiparallel to the field (high energy or "spin down" nuclei, see Figure 1F) There are always more spin up nuclei than spin down, but the more powerful the field, the larger the proportion of spin up nuclei. At this point more of the hydrogen nuclei have lined up parallel than antiparallel to the field and this results in the patient having a Net Magnetisation Vector.

Figure 1F: **Alignment of hydrogen nuclei under the influence of an external magnetic field (Bo) resulting in a net magnetisation vector (NMV)**



1.5.2.3 Precession and resonance

There is always a degree of wobble of the NMV around the axis of the magnetic field, which is termed precession. The precessional frequency (also called the Larmor frequency) is defined by the Larmor equation as follows:

Precessional frequency = Bo x γ where γ is the gyromagnetic ratio which is a constant for a specific MR active nucleus at 1.0 Tesla

Precession is important because it gives hydrogen nuclei the ability to resonate in response to pulses of radiofrequency energy, if delivered at exactly the Larmor frequency. Energy is absorbed and some low energy "spin up" nuclei become high energy "spin down" nuclei. This is termed Nuclear Resonance or excitation, and has two effects:

1) The axis of the patient NMV shifts from the longitudinal plane by a variable degree known as the Flip angle, usually by a full 90° into the transverse plane.
2) Each individual hydrogen nuclear magnetic moment making up the patient NMV begins to precess in phase.

1.5.2.4 The MR signal

The NMV is therefore precessing in the transverse plane, creating a moving magnetic field. According to Faraday's laws of induction, a voltage will be induced in a receiver coil placed in a moving magnetic field. The voltage induced in such a coil by the precessing NMV constitutes the MR signal and is the basis for MRI. A Pulse Sequence of energy at Resonance Frequency (RF) is delivered to the Hydrogen nuclei under the

influence of the magnetic field, and MR signals are detected in multiple receiver coils located in the scanner, which allows a three dimensional image to be constructed.
When the energy pulse ends, the patient NMV begins to realign itself once more with the magnetic field. Magnetisation in the longitudinal plane increases (termed T1 Recovery) and in the transverse plane decreases (T2 Decay), both in an exponential way. The degree of T1 Recovery and T2 Decay that take place depends upon the following:

Repetition Time (TR): The time in milliseconds between pulses of energy which determines the amount of T1 Recovery that has time to occur.

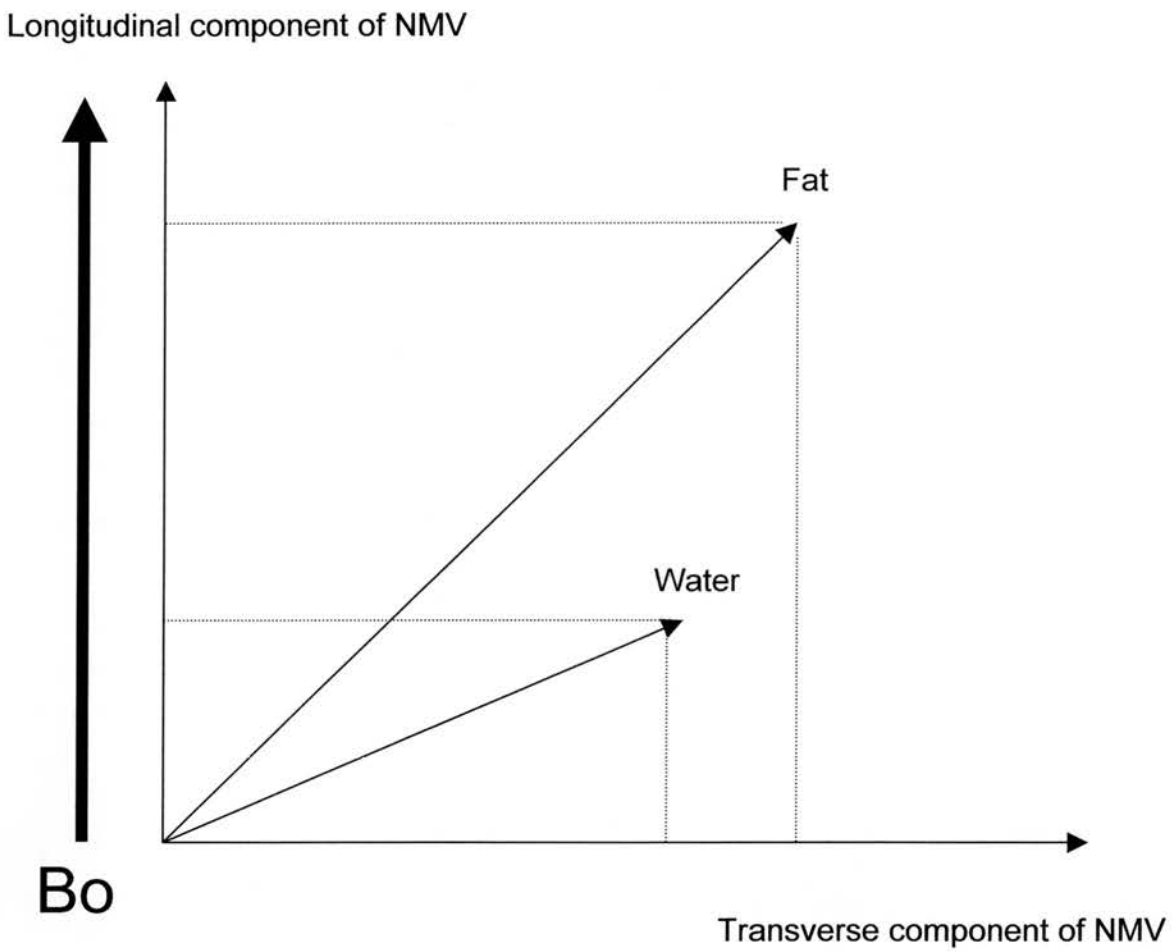
Echo Time (TE): The time in milliseconds from the onset of an energy pulse to the time of peak signal induction in the coil, thus defining the amount of T2 Decay that has time to take occur.

Each pulse sequence is defined by these two separate timing parameters.

1.5.2.5 How is contrast generated?

The NMV can be divided into longitudinal and transverse components. If the NMV of a tissue has a relatively large transverse component than it will induce a higher voltage in the receiver coil resulting in a bright (or white) area on the image. Similarly a small transverse component results in a dark (or black) area on the image. The Larmor frequency of hydrogen in fat is lower than in water, resulting in a difference in NMV between these two tissues and a different MR signal intensity (Figure 1G). Most soft tissues are made up varying degrees of fat and water, explaining the exceptionally good resolution that can be obtained with MRI.

Figure 1G: **Contrast is generated by the difference in transverse and longitudinal components of NMV between fat and water**



As described above, the operator can determine the amount of T1 Recovery and T2 Decay that takes place by setting the TR and TE appropriately:

T1 weighting (bright fat)	Short TR	(increases T1)
	Short TE	(decreases T2)
T2 weighting (bright water)	Long TR	(decreases T1)
	Long TE	(increases T2)

Furthermore, tissues with higher proton density (eg: brain) induce a larger voltage in the receiver coil, and therefore generate brighter images. Proton density images can be obtained with the following settings:

Proton density weighting	Long TR	(decreases T1)
	Short TE	(decreases T2)

In summary, contrast depends upon the intensity of the MR signal generated, and this in turn essentially depends upon three factors: T1 weighting, T2 weighting and Proton density.

1.5.3 General points

Magnetic Resonance Imaging is an attractive modality for studying the complex geometry of the right ventricle and pulmonary vasculature since no assumptions need to be made about the shape or location of the structure being studied. It provides three-dimensional anatomical measurements of right ventricular morphology that are unaffected by physiological variables and more likely to be reproducible than dynamic, planar measurements made at echocardiography. Furthermore, these anatomical variables reveal the right ventricular response to chronic pulmonary vascular disease and may provide a more clinically relevant assessment of disease severity.

MRI has been extensively used to image the left ventricle but there have been relatively few studies of right ventricular function and morphology. It has been successfully used to quantify ventricular volumes and estimate ventricular mass in both normal and PAHT subjects and normal ranges have been established (118-122). Clear abnormalities have been demonstrated both in right ventricular morphology and function and in the proximal pulmonary vasculature in PAHT (121-125). Non-invasive assessments of blood flow and distensibility in the pulmonary arteries can be made (126-128), as well as estimates of stroke volume and cardiac output (127). Changes in right ventricular mass, function and pulmonary artery blood flow have been observed following lung transplantation (129-132), and MRI has been shown to be far more accurate than echocardiography in monitoring changes in left ventricular mass (133).

1.5.4 Pulmonary artery pressure

Several investigators have attempted to use MRI as a non-invasive means of estimating mean pulmonary artery pressure (MPAP) using a number of different approaches. Some studies have reported a "slow flow" phenomenon, with persistent high MR signal intensity in the pulmonary arteries during systole (123, 125, 134, 135). Didier and Higgins studied this phenomenon in 15 patients with congenital left to right shunts and 10 normal volunteers. They demonstrated a linear relationship between the intensity of the MR signal in systole in the right pulmonary artery and pulmonary vascular resistance (PVR) in those with elevated pulmonary artery pressure. There was an even closer correlation with the ratio of PVR over systemic vascular resistance (135). Similarly, Von Schultess et al reported a good correlation with PVR in PPH (134).

The right ventricle hypertrophies in response to raised pulmonary artery pressure. Right ventricular end-diastolic wall thickness (RVWT) has been shown to correlate well with MPAP and PVR in PPH and some causes of secondary pulmonary hypertension including chronic lung disease, left heart disease and chronic pulmonary embolism (123, 125, 136). Saito et al reported close correlations with MPAP for RVWT and the ratio of RVWT divided by left ventricular posterior wall thickness (LVPWT) in 36 patients with chronic lung disease and a range of MPAP from 10-50 mmHg (136). Frank et al

demonstrated a good correlation with RVWT corrected for body surface area (BSA) in 23 patients with MPAP range 37-75 mmHg (125).

With hypertrophy comes an increase in mass and a linear relationship between right ventricular mass (RVM) and MPAP has been described for PPH (122). In the largest series in the literature, Katz et al measured RVM using MRI in 13 subjects with a diagnosis of PPH, five of whom were under 18 years of age. They used a modified Simpsons rule to calculate right and left ventricular mass (see General Methods), a method which they validated by initially scanning and then weighing ten fresh calf hearts. They derived a right ventricular mass index by correcting for BSA and demonstrated a good correlation with an r value of 0.75 with MPAP using linear regression analysis (122). Using a similar method, Turnbull et al reported a correlation of 0.72 between RVM and MPAP in 16 subjects with moderate/severe COPD with MPAP 30 +/- 10 mmHg (137).

An alternative approach has been to measure the diameters of the great vessels. This was based upon the theory that raised pulmonary artery pressures would lead to proportional distension of the pulmonary arteries and great veins emptying into the right atrium, and furthermore that the consequent reduction in cardiac output would result in reduced aortic diameter. Studies have reported correlations between MPAP and main pulmonary artery diameter (MPAD) (125, 138-141) and diameter of inferior vena cava (125). Murray et al measured the ratio of MPAD over descending Aortic diameter (MPAD/AOD) in 12 patients with PPH (MPAP 59.6 +/- 19.0 mmHg) within one week of cardiac catheterisation (124). Although overall agreement was poor, they were able to report an r value of 0.7 for MPAD/AOD due to the wide range of MPAP in their study population. Ng et al reported the results of a similar study using CT in 50 patients with a wide range of pulmonary and cardiovascular diseases and found a strong correlation between MPAD/AOD and MPAP, especially in patients younger than 50 years(139).

1.5.5 Cardiac output

Two main approaches have been used to measure cardiac output using MRI: firstly by calculation of stroke volume and ejection fraction using Simpsons rule by subtracting

systolic ventricular volume from diastolic ventricular volume, and secondly by measuring blood flow through the great vessels or the cardiac valves. Studies have been limited by the difficulty in obtaining simultaneous invasive measurements of cardiac output since conventional thermodilution cardiac catheters and monitors are not MR compatible. Nevertheless, a number of studies have demonstrated good agreement with recently acquired invasive measurements using both methods.

Simpsons rule

Several studies have shown that MRI is accurate and reproducible for estimation of both left and right ventricular volumes in normal and abnormal subjects (119, 142-152), and is probably superior to conventional echocardiography (153, 154). Some investigators did experience difficulty outlining the right ventricle (151), and in pulmonary hypertension intra- and inter-observer errors seem to be greater, in particular for the right ventricle. Boxt et al reported a right to left ventricular stroke volume ratio of 3.17 to 1 due to tricuspid regurgitation with reduced reproducibility of both left and right ventricular measurements (120). Hoeper et al found that this method of calculating cardiac output constantly overestimated the cardiac output for the same reason (155).

Blood flow

There has been more success with methods that derive cardiac output by measuring blood flow through the aorta or main pulmonary artery. The use of MRI velocity mapping to measure blood flow has been extensively validated in phantom, animal and human subjects (see Chapter 7)(156-163). Tardivon et al reported a good correlation for right cardiac output and stroke volume between MRI and cardiac catheterisation in PPH, however agreement between the two was poor (127). Hoeper et al studied 16 patients with primary or thromboembolic pulmonary hypertension and found good agreement for right cardiac output between MRI and catheterisation in all but two subjects (155). Mousseaux et al reported similar findings in a study of 19 subjects, 12 with primary or secondary pulmonary hypertension and 4 post-cardiac transplant (164).

1.6 Aims of research

As discussed, clinical and study endpoints have always focussed on changes in pulmonary haemodynamics and exercise tolerance as a means of monitoring patients with pulmonary hypertension. Our aim was to investigate an alternative strategy; studying the adaptation response of the heart and pulmonary vasculature to pulmonary hypertension. There have been surprisingly few published attempts to study the effects of treatment on the morphology of the right heart and pulmonary circulation using echocardiography. Barst found improvements in right ventricular function and interventricular septal movement following calcium channel blockers and phenoxybenzamine (165). Rich and Brundage reported a reduction in right ventricular chamber size and normalisation of the systolic interventricular septal curvature in a small group of patients treated with calcium channel blockers (19). Hinderliter et al also demonstrated less right ventricular dilatation and improved septal curvature following twelve weeks of continuous intravenous prostacyclin (29).

Modern advances in cross-sectional imaging, in particular Magnetic resonance imaging (MRI), have made it possible to make anatomical and physiological measurements in the cardiorespiratory system with a high degree of accuracy and reproducibility. We chose MRI for this study, because the lack of radiation exposure and contrast injection makes it more suitable for repeated studies than CT.

Anatomical measurements made with MRI are accurate and reproducible. Unlike haemodynamic measurements they are not influenced by variation in short-term physiological factors such as hydration status, posture, heart rate or oxygen saturation. Therefore changes in these measurements may reflect the effect of sustained rises in pulmonary artery pressure. In other words they may measure the response of the right ventricle and pulmonary circulation to longstanding pulmonary vascular disease. If this is the case, they may provide the pulmonary vascular physician with an accurate non-invasive means of monitoring disease progression and the response to treatment. An analogy can be made with the use of glycosylated haemoglobin in monitoring patients with diabetes, where the HbA1c provides an assessment of glucose level over the previous few months (166). The rate of change of these variables may also provide useful

prognostic information, and help with treatment decisions, in particular the difficult decision of when to list for transplantation. MRI can also provide measurements of blood flow in the pulmonary circulation quickly and accurately, which may also provide a means of monitoring the "burden of disease" over time.

Our aim in this thesis was to develop indices that may be useful in this alternative approach to the assessment of patients with pulmonary hypertension, derived from anatomical and physiological measurements made with MRI. We then studied the accuracy of these indices in detecting and quantifying pulmonary artery pressure at right heart catheterisation, and any potential advantages over doppler echocardiography, the current gold standard noninvasive investigation. Long term follow-up studies to test the accuracy of this approach were beyond the scope of this thesis due to time constraints.

2 General methods

2.1 Study protocol

Patients were usually admitted to the Scottish Pulmonary Vascular Unit (SPVU) for investigation or reassessment on a Monday and discharged on a Friday. One or two patients were admitted every week and underwent a series of pre-booked investigations (Table 2A) including right heart catheterisation on a Thursday. Management decisions were made on a Friday before discharge.

Table 2A: Routine investigation at Scottish Pulmonary Vascular Unit

Venous bloods	Urea and electrolytes Full blood count Liver function tests Thyroid function tests Glucose Scleroderma autoantibody screen Thrombophilia screen Human immunodeficiency virus serology Hepatitis B and C serology
Arterial blood gases	
Chest radiograph	
High resolution CT scanning	
Ventilation/Perfusion scanning or CT pulmonary angiography	
Doppler echocardiography	
Pulmonary function tests	
Six minute walk test	
Right heart catheterisation	

The study protocol is shown in Table 2B. Consent was sought shortly after admission. MRI and doppler echocardiography (Echo) were performed as soon after right heart catheterisation (RHC) as possible in those unable to follow the schedule for logistical or personal reasons.

Table 2B: Study Protocol

	a.m.	p.m.
Monday	Enrolment	
Tuesday	Echocardiography	
Wednesday	Six minute walk test	Magnetic resonance imaging
Thursday	Right heart catheterisation	
Friday	Analysis of data	

2.2 Study subjects

2.2.1 Recruitment

This study was approved by West Glasgow Hospitals NHS Trust Ethics Committee. All patients referred to the SPVU for investigation or reassessment of suspected pulmonary hypertension between September 1999 and March 2001 were considered for enrolment. Subjects who had previously been enrolled were not studied a second time.

Consent forms and Patient Information Sheets are reproduced in Appendix 1. It can be seen that this was part of a larger study run by the SPVU comparing the data obtained from ambulatory pulmonary artery monitoring, cardiopulmonary exercise testing and magnetic resonance imaging. We have only submitted the MRI data in this thesis.

2.2.2 Demographics

Twenty-eight subjects (nine male, nineteen female) were enrolled after informed consent was obtained (Table 2C). All had normal left ventricular function and morphology at echocardiography.

PAHT was confirmed in twenty-one subjects (Table 2C), of whom seven had PPH, five connective tissue disease (CTD), three congenital heart disease (CHD), two chronic obstructive pulmonary disease (COPD), two portopulmonary disease (PP), one chronic thromboemboembolism (CTEPHT) and one hereditary haemorrhagic telangiectasia (HHT). Seven subjects had normal pulmonary haemodynamics at RHC, and had been referred because of evidence at Echo (subjects 4,6,11,12,25) or cardiopulmonary exercise testing (subjects 14,23) coupled with a strong clinical suspicion of PAHT.

2.3 Conventional assessment of pulmonary haemodynamics

2.3.1 Right heart catheterisation

2.3.1.1 Method

This was performed according to our standard protocols using a balloon-tipped, thermodilution, cardiac catheter (Swan Ganz, 7-F, Baxter Healthcare, Irvine, CA, USA). Pressures were recorded in the right atrium, right ventricle and proximal pulmonary artery and an estimate of pulmonary artery occlusion pressure was made with the catheter in the wedge position. Cardiac output was averaged over a minimum of three measurements made by thermodilution except for those with shunting when the direct Fick method was used (subjects 8,10,15). Measurements were made on supplementary oxygen for those on long term oxygen therapy (subjects 16,17,20,21). Pulmonary hypertension was defined as a MPAP of 25 mmHg or more (5).

Table 2C: Subject demographics and diagnoses

	Sex	Age (yrs)	BSA	Diagnosis	MPAP (mmHg)	CO (L/min)	PAOP (mmHg)	Echo PASP (mmHg)
1	F	40	2.01	PPH$^{\alpha}$	52	3.4	*	58
2	M	42	1.67	PPH	63	3.3	14	144
3	M	51	1.68	CTD	40	3.5	8	64
4	F	53	1.61	No PAHT	16	5.7	11	49
5	F	56	1.51	PPH	61	3.7	7	112
6	F	32	1.61	No PAHT	19	5.1	8	< 25
7	F	50	1.98	CTEPHT	27	3.9	9	41
8	F	38	1.40	CHD	78	5.5	4	**
				Eisenmengers VSD				
9	M	29	2.00	PP	36	6.7	8	52
10	F	44	1.77	CHD	66	4.7	*	121
				Eisenmengers ASD				
11	F	54	1.72	No PAHT	15	6.0	7	36
12	F	42	1.51	No PAHT	19	4.1	10	16
13	F	58	1.82	PPH$^{\alpha}$	31	4.6	12	25
14	F	64	1.47	No PAHT$^{\beta}$	16	4.4	6	27
15	F	33	1.63	CHD	78	6.2	9	74
				Eisenmengers VSD				
16	M	58	1.92	CTD$^{\beta\chi}$	44	2.7	*	88
17	F	61	1.40	CTD$^{\chi}$	34	2.8	4	100
18	M	62	1.95	PPH$^{\alpha}$	53	3.6	13	104
19	M	51	1.86	COPD	29	3.7	12	52
20	M	60	2.00	COPD$^{\beta\chi}$	39	4.8	14	50
21	M	66	1.83	PPH$^{\chi}$	40	2.6	7	74
22	F	31	1.92	PP	41	6.3	10	***
23	F	48	1.83	No PAHT	16	3.4	11	23
24	F	68	1.75	CTD	35	5.4	12	58
25	F	60	1.97	No PAHT	16	6.8	7	38
26	F	57	1.59	HHT	53	6.4	6	52
27	F	43	1.94	CTD	38	4.6	5	64
28	M	59	1.66	PPH	47	3.7	2	52

FOOTNOTES:

BSA = Body surface area, MPAP = Mean pulmonary artery pressure, CO = Cardiac output, Echo = Doppler echocardiography, PASP = pulmonary artery systolic pressure, PAHT = Pulmonary arterial hypertension, PAOP = pulmonary artery occlusion pressure, PPH = Primary pulmonary hypertension, CTD = Connective tissue disease, CTEPHT = Chronic thromboembolic pulmonary hypertension, CHD = Congenital heart disease, PP = Portopulmonary hypertension, HHT = Hereditary haemorrhagic telangiectasia. $^{\alpha}$ = Systemic hypertension, $^{\beta}$ = Ischaemic heart disease, $^{\chi}$ = Long term oxygen therapy * = PAOP unobtainable, ** = High pressure but unquantifiable, *** = No tricuspid regurgitation so unable to estimate pressure

2.3.1.2 Results

Measurements were successfully obtained in all twenty-eight subjects and the results are shown in Table 2C. There was a wide range of MPAP (15-78 mmHg) and CO (2.6-6.8 L/min) and statistically significant differences between normal subjects and those with raised pulmonary artery pressure for all variables (Table 2D). PAOP was normal (ie:<15 mmHg) in all subjects except 1, 10 and 16 in whom it could not be measured for technical reasons. There were no major complications.

Table 2D: Comparison : Normals vs PAHT

	NORMALS (n=7)		PAHT (n=21)		
	Mean	Range	Mean	Range	p-value
AGE (yrs)	50 ± 11	32-64	50 ± 12	29-68	NS
BSA	1.67 ± 0.18	1.47 – 1.97	1.78 ± 0.2	1.4 – 2.01	NS
MPAP (mmHg)	17 ± 2	15-19	47 ± 15	27-78	< 0.0001
CO (L/min)	5.1 ± 1.2	3.4-6.8	4.4 ± 1.3	2.6-6.7	NS
PASP (Echo) (mmHg)	31 ± 11	16-49	73 ± 31	25-144	< 0.0001

FOOTNOTES:

BSA = Body surface area, MPAP = Mean pulmonary artery pressure, CO = Cardiac output, Echo = Doppler echocardiography, PASP = pulmonary artery systolic pressure, PAHT = Pulmonary arterial hypertension, NS = not significant

2.3.1.3 Discussion

Our subject group and cardiac catheterisation results are similar to those reported by other centres specialising in the investigation of pulmonary vascular disease (11).

2.3.2 Doppler echocardiography

2.3.2.1 Method

Pulmonary artery systolic pressure (PASP) was estimated from tricuspid regurgitation in the conventional way (Acuson Sequoia c256, Mountain View, CA, USA) as described in the Introduction. Standard assessments of cardiac chamber size, valvular competence and right and left ventricular function were also made. All measurements were made by the same experienced echocardiographer who was not aware of the results of cardiac catheterisation. Measurements were made on supplementary oxygen for those on long term oxygen therapy.

The senior echocardiographer, who performed all of the measurements included in this thesis, reported PASP without correcting for estimated right atrial pressure. We chose to define pulmonary hypertension as a PASP of > 35mmHg, which corresponds with a tricuspid regurgitation jet velocity of > 3.0 m/s assuming right atrial pressure to be zero. This is the definition suggested by Yock and Pop when they first described this method (65), however, there has been disagreement on the correct definition in the literature since then, with many authors choosing to define pulmonary hypertension as a PASP of > 40 mmHg. Unfortunately it is often unclear whether this includes right atrial pressure, making direct comparison difficult. Ideally, actual measurements of tricuspid regurgitation jet velocity should be reported, to remove any ambiguity, however this has not been the case historically. In any case, this would have no effect on most of the correlations reported in this thesis.

2.3.2.2 Results

All twenty-eight subjects underwent doppler echocardiography within two days of cardiac catheterisation except 27 and 28 in whom the interval was four weeks. The values for estimated PASP are shown in Table 2C and ranged from 16 to 144 mmHg. Values are listed for twenty-five subjects; subject 6 was reported as " < 25 " and a value of 25 was used for statistical analysis. In subject 8, estimated PASP was raised but could not be

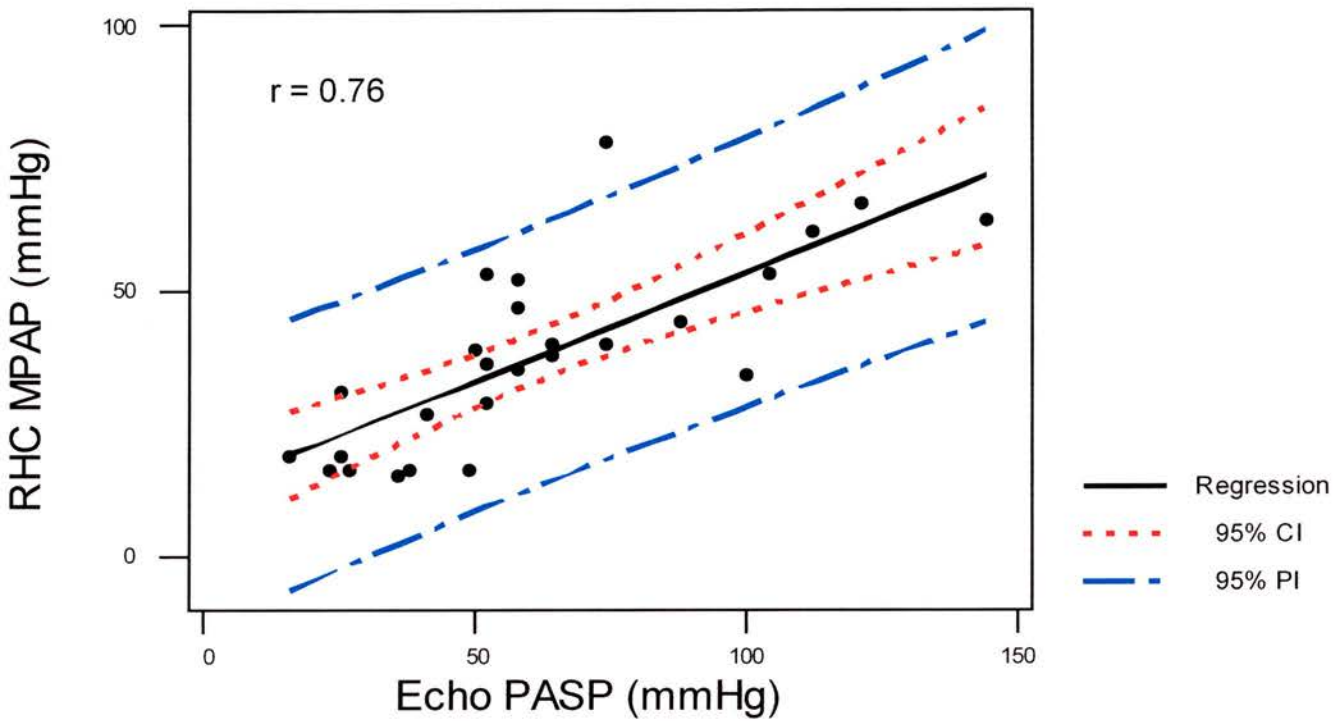
accurately measured, and was therefore not included in linear regression analysis. PASP could not be measured in subject 22.

There was a significant difference between the normal subjects and those with pulmonary hypertension ($p < 0.0001$ Table 2D) and a good correlation with MPAP as shown in Figure 2A ($r = 0.76$). However there were three false positive results (subjects 4,11 and 25), one failed scan (subject 22) and one false negative result (subject 13), giving an overall sensitivity of 90% and a specificity of 57%.

2.3.2.3 Discussion

Our results are broadly in line with the published literature regarding the accuracy and limitations of doppler echocardiography for the estimation of pulmonary artery pressure. Similar correlations have been reported in several studies (74). Our failure rate was lower than previously reported; in particular both of our subjects with COPD were successfully scanned (78, 87). There have been reports of both false positive and false negatives, although it should be noted that all our normal subjects had been referred with a high index of clinical suspicion of pulmonary vascular disease, five with an abnormal echocardiogram.

Figure 2A: Correlation between RHC and Echo



RHC = right heart catheterisation, Echo = doppler echocardiography, MPAP = mean pulmonary artery pressure, PASP = pulmonary artery systolic pressure, CI = confidence intervals, PI = prediction intervals

2.4 Magnetic resonance imaging

2.4.1 General protocol

MRI scans were performed using a standard scanner (Impact Expert 1.0 T, Siemens Medical Engineering, Erlangen, Germany, see Figure 2B). Imaging sequences broadly followed the protocol described by Marcus et al (118). A coronal section was performed through the chest and from this "scout" sequence a horizontal cross-sectional view was obtained through the base of the heart showing the main pulmonary artery and descending aorta. From this image we obtained a series of cross-sectional images from the bifurcation of the main pulmonary artery to the right ventricular outflow tract at ten millimetre intervals (Figure 2C, Sequence A). Image acquisition was triggered by the ECG R wave resulting in a stack of images at each slice position. Main parameters were T1 weighted SE with TR approximately 700ms, TE 30, slice thickness 10 mm, Flip Angle 90 degrees. To optimise scan time each slice was acquired at a different point in the cardiac cycle using an interleaved 45ms interval. From the initial coronal "scout" sequence a horizontal long-axis view was then obtained showing the four chambers of the heart. A series of short-axis images were then acquired perpendicular to the long-axis view, starting at the tricuspid valve and covering the complete right ventricle from base to apex (Figure 2C, Sequence B). Finally the initial coronal "scout" sequence was used to find the long axis of the right pulmonary artery as it passes beneath the arch of the aorta with a series of cross-sectional and coronal images to confirm the position of the vessel (see Chapter 7 Figures 7A-7C). An oblique sagittal image was then used to perform a flow quantification in the right pulmonary artery. This was repeated after exercise in selected subjects (see Chapter 8).

Short-axis image acquisition was triggered by the ECG R wave and performed in cine mode with a temporal resolution of 55 milliseconds, resulting in a series of images during the cardiac cycle at 55 ms intervals at each slice position. This was done by a segmented Flash with view-sharing to allow a reduced time resolution. Main parameters were TR 110, TE 6.1, slice thickness 10 mm, Flip Angle 20 degrees.

Figure 2B: Magnetic resonance imaging

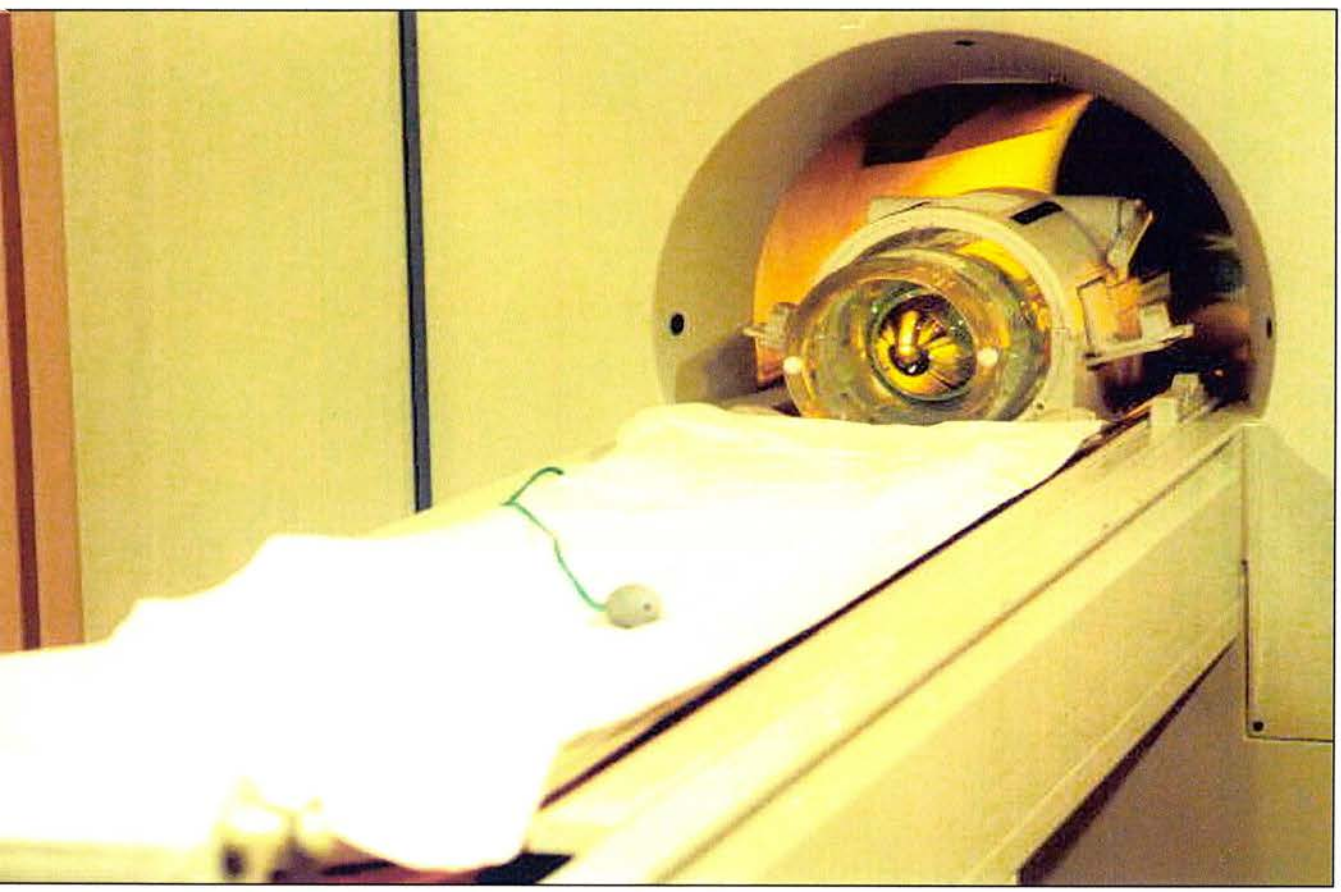
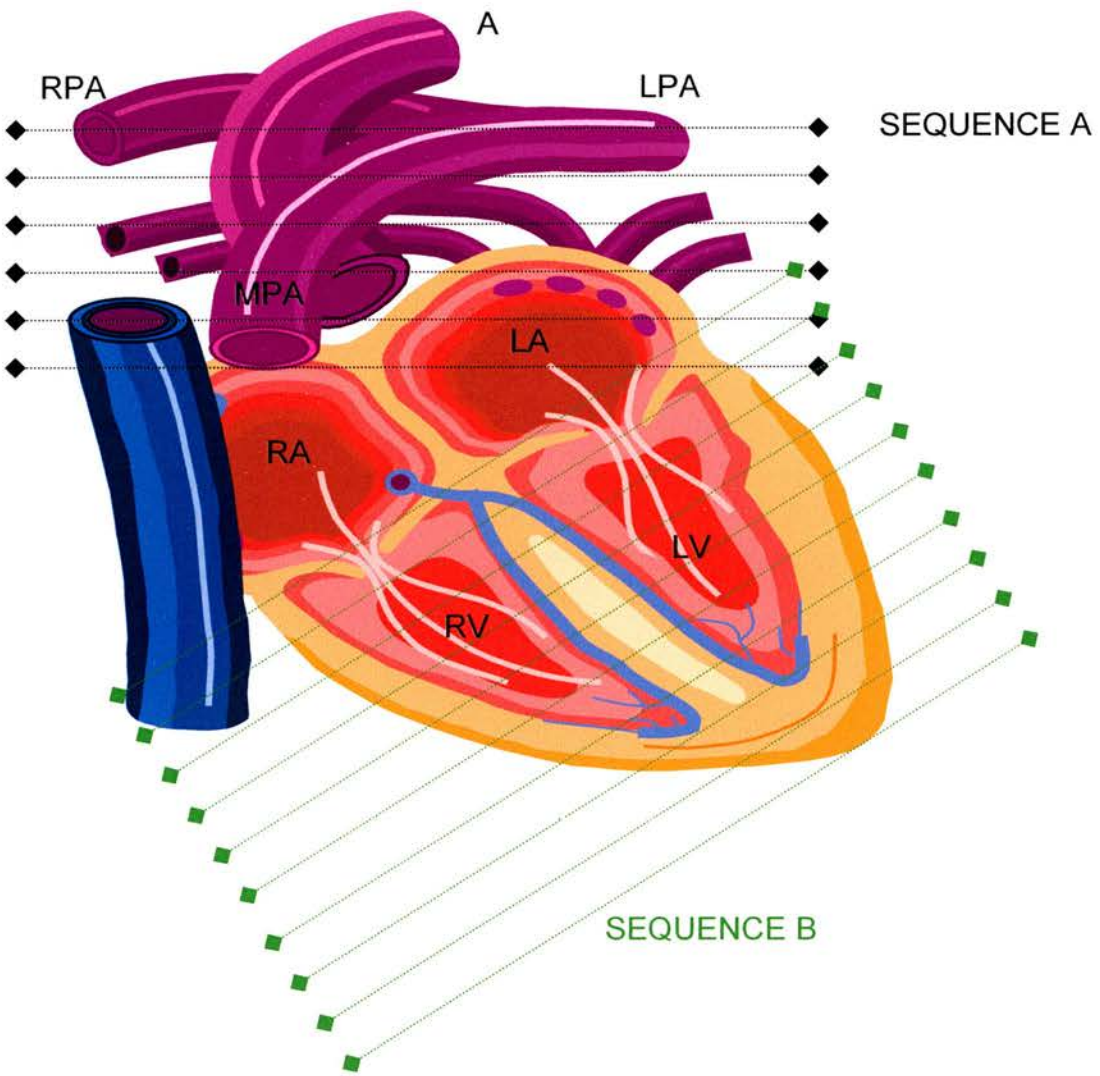


Figure 2C: MRI scanning protocol



RA = right atrium, LA = left atrium, RV = right ventricle, LV = left ventricle, MPA = main pulmonary artery, A = aorta, RPA = right pulmonary artery, LPA = left pulmonary artery

Fifteen consecutive heartbeats were required to acquire a set of images in each plane. Subjects were instructed to hold their breath during the acquisition of short-axis images of the ventricles. This resulted in a 12 to 15 second breathhold for image acquisition in each short-axis slice position and six to eight slices were required per patient. Subjects were instructed to breathhold at end-expiration because breathholding at deep inspiration has been reported to diminish cardiac output by up to 40% in normal subjects (167-169). A flow quantification was performed in the right pulmonary artery at rest in all subjects and after exercise in a proportion. The method is described later in the relevant chapters (sections 7.2 and 8.2). Studies were performed without supplementary oxygen for logistical reasons.

2.4.2 Study subjects

Twenty-two out of twenty-eight subjects underwent MRI within two days of RHC. The remaining six were scanned up to two weeks later (subjects 1,2,6,15,19 and 21). Scanning was incomplete in one subject who was unable to breathhold adequately and has since died (subject 16), and was abandoned in another subject due to acute claustrophobia (subject 7).

2.4.3 Image analysis

The following measurements were made: Right and Left Ventricular Mass (RVM, LVM, see Chapter 3), Right and Left ventricular end-diastolic volume (RVEDV, LVEDV, see Chapter 4), Right Ventricular End-Diastolic Wall Thickness (RVWT) and Left ventricular posterior wall thickness (LVPWT, see Chapter 5), Main Pulmonary Artery diameter (MPAD) and diameter of descending Aorta (AOD, see Chapter 6), Mean and Peak velocity in the right pulmonary artery (MV, PV, see Chapters 7 and 8). The calculation of each measurement is described in the relevant chapter. The raw data is tabulated in Appendix 2.

The first image acquired after R wave triggering was considered to best represent end-diastole and used to calculate RVM, LVM, RVEDV, LVEDV, RVWT and LVPWT. The cross-sectional images used to measure MPAD and AOD were not ECG gated.

2.5 Statistical analysis

Data was analysed using Minitab for Windows (Release 12.1). Pearson's correlation coefficient and linear regression analysis were used to assess the relationship between MPAP measured at RHC and measurements made at Echo and MRI. Where appropriate, subjects were also divided into those with normal MPAP at RHC (Normals) and those with raised MPAP (PAHT). The 2 sample t test was used to assess the significance of differences between the two groups. An "intention to scan" analysis was done when calculating sensitivities and specificities unless otherwise indicated.

3 Ventricular mass

3.1 Introduction

As discussed earlier, a linear relationship between right ventricular mass and MPAP has been described in PPH but not for other forms of PAHT (122). In our first study we investigated whether a new Ventricular Mass Index measured with MRI and not previously described in PAHT can provide an accurate means of estimating MPAP non-invasively in subjects with both PPH and a wide range of types of secondary PAHT undergoing routine invasive RHC. We then compared the accuracy of these estimates with those made at Echo.

3.2 Method

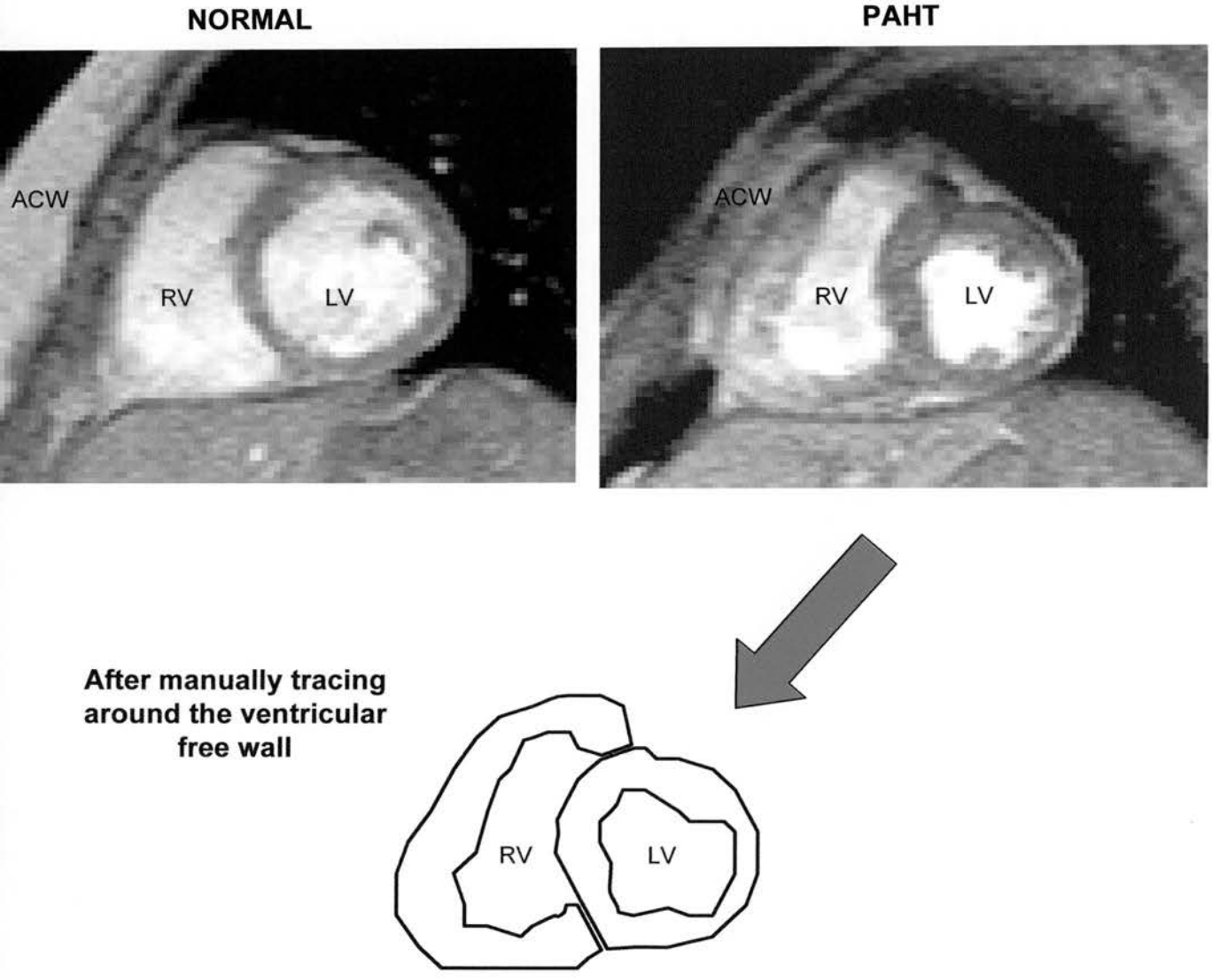
3.2.1 Study subjects

Subjects were recruited as outlined in Chapter 2 and are shown in Table 2C. Subjects 27 and 28 were not included in this study because the interval between RHC and Echo of four weeks was considered to be too long to make an accurate comparison.

3.2.2 MRI image analysis

RVM and LVM were calculated using a modified Simpsons rule as follows (118, 122): The interventricular septum was taken to be part of the left ventricle. The cross-sectional area of right ventricular myocardium in each end-diastolic short-axis slice was calculated by manually tracing around the interior and exterior of the right ventricular free wall (see Figure 3A). The total volume of muscle for that slice was then obtained by multiplying the cross-sectional area by the slice thickness. This process was repeated for each short-axis slice and the total volume of right ventricular myocardium calculated by summing all the slice volumes (Figure 1E). RVM was then derived by multiplying the total volume by the specific density of cardiac muscle ($1.05 g/cm^3$). The moderator band was included

Figure 3A: Short-axis images of ventricles used to calculate RVM and LVM



RVM = right ventricular mass, LVM = left ventricular mass,
ACW = anterior chest wall, RV = right ventricle, LV = left ventricle

in the calculation for RVM where it appeared. The process described above was repeated for the left ventricle to calculate LVM except that the cross-sectional area of myocardium in each slice was calculated by subtracting the area of the internal polygon from the external (see Figure 3A). Our new Ventricular Mass Index (VMI) was obtained by dividing RVM by LVM to correct for variation in body habitus, a technique used in animal models of pulmonary hypertension (170), but not previously used in man. A further ventricular mass index was obtained by dividing RVM by BSA, as described by Katz et al (122).

3.2.3 Statistical analysis

Data was analysed using Minitab for Windows (Release 12.1). Pearson's correlation coefficient and linear regression analysis were used to assess the relationship between MPAP measured at RHC and measurements made at Echo and MRI. Where appropriate, subjects were also divided into those with normal MPAP at RHC (Normals) and those with raised MPAP (PAHT). The two sample t test was used to assess the significance of differences between the two groups. An "intention to scan" analysis was done when calculating sensitivities and specificities.

3.3 Results

3.3.1 Ventricular mass

The mean calculated values for RVM, LVM and VMI are shown in Table 3A for twenty-four subjects. Measurements were not possible in subject 16 due to difficulty breath-holding and subject 7 due to claustrophobia. There was a significant difference between the two groups for RVM ($p<0.005$) and VMI ($p<0.01$), but not for LVM. There was a weak correlation between MPAP and RVM ($r = 0.56$, Figure 3B), which improved after correcting for BSA ($r = 0.65$, Figure 3C) but a much stronger correlation with reduced scatter between MPAP and VMI, ($r = 0.81$, Figure 3D). If we take a VMI of > 0.6 as abnormal there was one false negative result (subject 24) and two false positives (subjects

4,25) with two scanning failures (subjects 7,16), giving a sensitivity of 84% and a specificity of 71% (Table 3B).

Table 3A: Comparison : Normals vs PAHT

	NORMALS (n=7)		PAHT (n=19)		
	Mean	Range	Mean	Range	p-value
AGE (yrs)	50 ± 11	32-64	50 ± 12	29-68	NS
MPAP (mmHg)	17 ± 2	15-19	47 ± 16	27-78	< 0.0001
CO (L/min)	5.1 ± 1.2	3.4-6.8	4.4 ± 1.3	2.6-6.7	NS
RVM (g)	66 ±24	31-107	126 ± 36	63-174	< 0.005
LVM (g)	129 ±24	98-172	145 ± 41	81-205	NS
VMI	0.5 ± 0.2	0.2-0.7	0.9 ± 0.2	0.6-1.4	< 0.01
Echo PASP (mmHg)	31 ± 11	16-49	75 ± 33	25-144	< 0.0001

FOOTNOTES:

BSA = Body surface area, MPAP = Mean pulmonary artery pressure, CO = Cardiac output, Echo = Doppler echocardiography, PASP = pulmonary artery systolic pressure, PAHT = Pulmonary arterial hypertension, NS = not significant, RVM = right ventricular mass, LVM = left ventricular mass, VMI = ventricular mass index

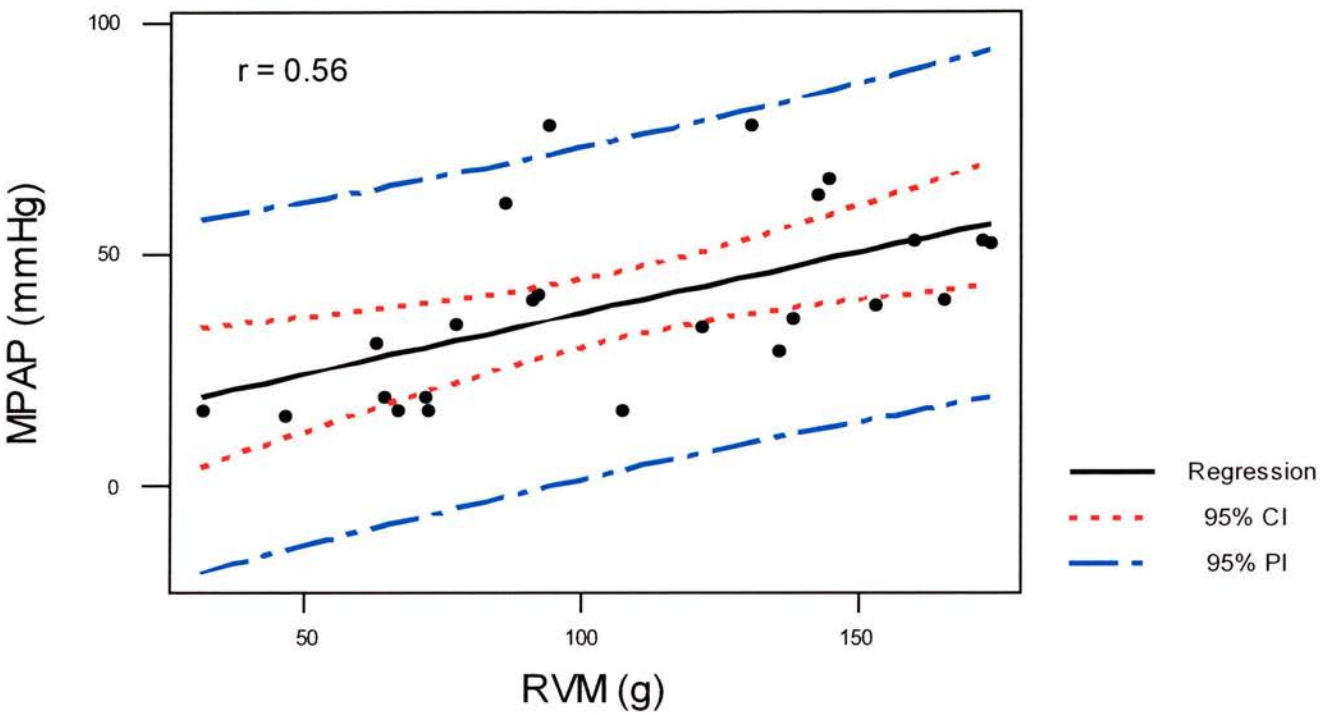
Table 3B: Correlations with MPAP and sensitivity and specificity for PAHT

		Correlation with MPAP	Sensitivity for PAHT	Specificity for PAHT
VMI	(n = 26)	r = 0.81	84 %	71 %
Echo PASP (mmHg)	(n = 26)	r = 0.77	89 %	57 %

FOOTNOTES:

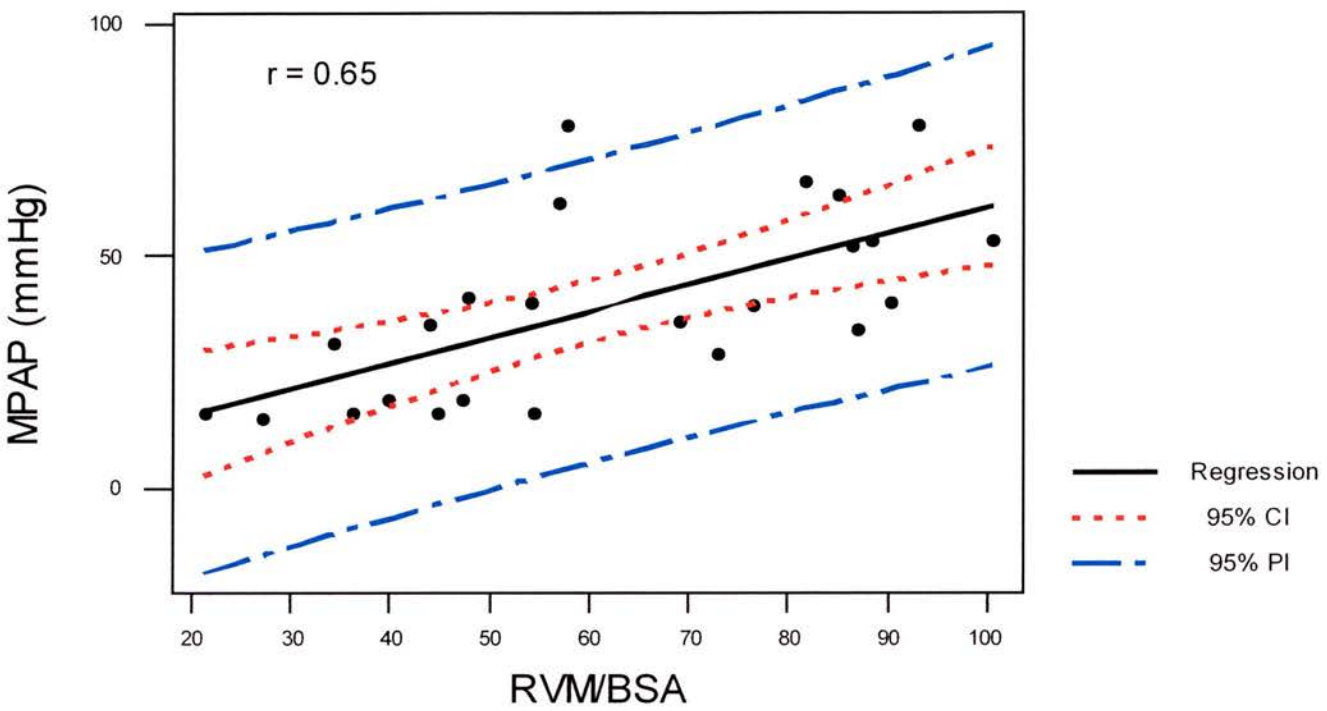
MPAP = mean pulmonary artery pressure, PAHT = pulmonary arterial hypertension, VMI = ventricular mass index, Echo = doppler echocardiography, PASP = pulmonary artery systolic pressure

Figure 3B: Correlation between MPAP and RVM



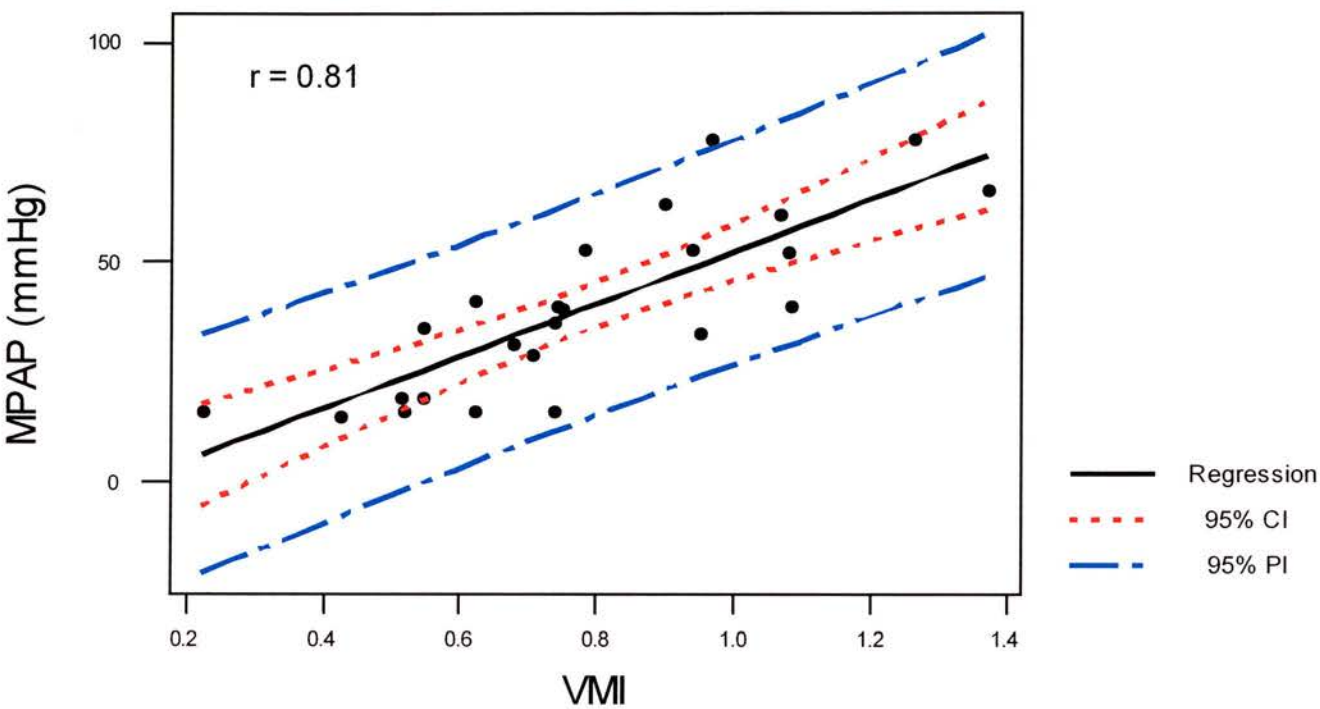
MPAP = mean pulmonary artery pressure, RVM = right ventricular mass,
CI = confidence intervals, PI = prediction intervals

Figure 3C: Correlation between MPAP and RVM/BSA



MPAP = mean pulmonary artery pressure, RVM = right ventricular mass,
BSA = body surface area, CI = confidence intervals, PI = prediction intervals

Figure 3D: Correlation between MPAP and VMI



MPAP = mean pulmonary artery pressure, VMI = ventricular mass index,
CI = confidence intervals, PI = prediction intervals

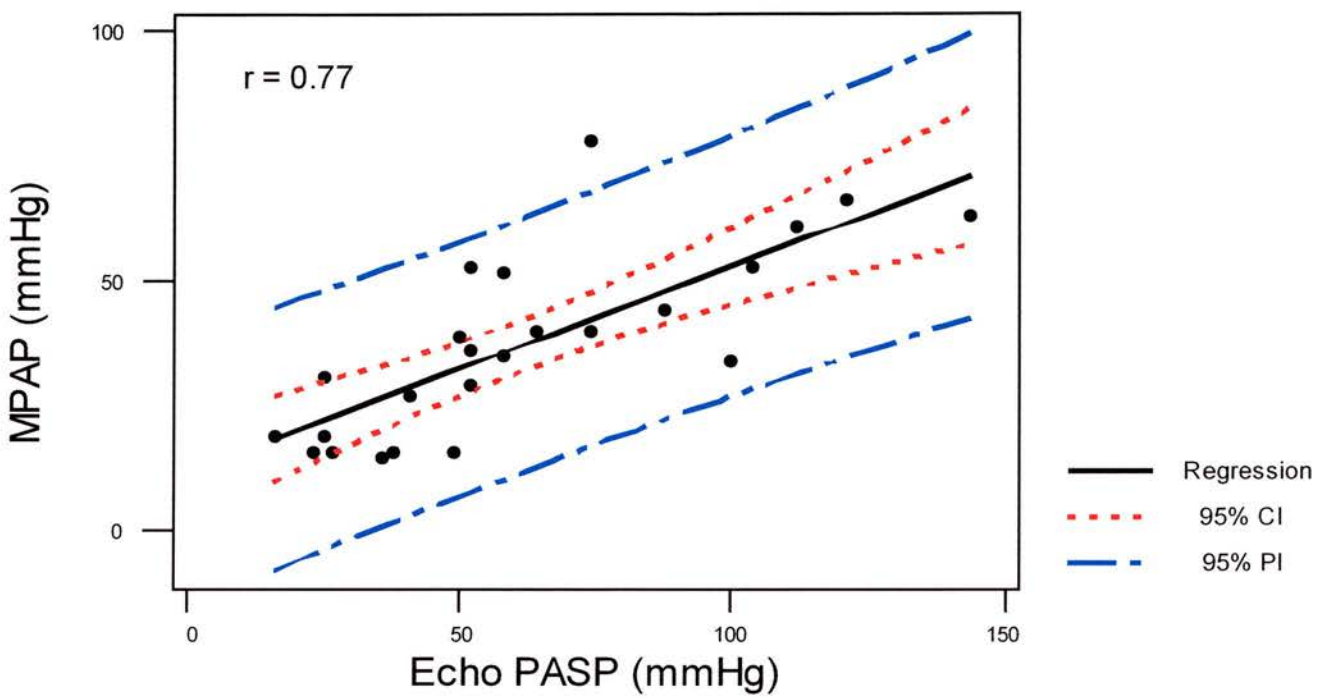
3.3.2 Doppler echocardiography

The values for estimated PASP are shown in Table 2C and statistical analysis in Tables 3A and 3B. Values are listed for twenty-four subjects; subject 6 was reported as " < 25 " and a value of 25 was used for statistical analysis. In subject 8, estimated PASP was raised but could not be accurately measured, and was therefore not included in linear regression analysis. PASP could not be measured in subject 22. There was a significant difference between the two groups ($p < 0.0001$) and a good correlation with MPAP as shown in Figure 3E ($r = 0.77$) and Table 3B. However there were three false positive results (subjects 4,11 and 25), one failed scan (subject 22) and one false negative result (subject 13), giving an overall sensitivity of 89% and a specificity of 57% (Table 3B).

3.4 Discussion

Our Ventricular Mass Index measured with Magnetic Resonance Imaging is a new clinical tool that provides an accurate and practical means of estimating mean pulmonary artery pressure non-invasively in subjects with Primary and Secondary pulmonary arterial hypertension with a wide range of pressures and diagnoses. Ventricular Mass Index correlated well with mean pulmonary artery pressure at right heart catheterisation, and although confidence and prediction intervals are relatively wide indicating limited precision, they are narrower than for echocardiography in the same group of subjects. The method we used for indexing Right Ventricular Mass has not been previously described in pulmonary hypertension. We found a closer agreement for our Ventricular Mass Index than for the method reported by Katz et al who devised a Right Ventricular Mass index calculated by dividing Right Ventricular Mass by Body Surface Area in a study of eight adults and five children with Primary Pulmonary Hypertension (122). We have also shown that our Ventricular Mass Index may be more specific for pulmonary arterial hypertension than Doppler Echocardiography, the current gold standard non-invasive investigation. This may be because pulmonary hypertension also has an effect on the morphology of the left ventricle (see Chapter 4). Ventricular Mass Index was also more

Figure 3E: Correlation between MPAP and Echo



MPAP = mean pulmonary artery pressure, Echo = doppler echocardiography,
PASP = pulmonary artery systolic pressure, CI = confidence intervals, PI = prediction intervals

sensitive than Doppler Echocardiography in those patients in whom scanning was successfully completed (94% versus 89% excluding subjects 7,16). This is the first study to suggest a practical advantage of magnetic resonance imaging over Doppler Echocardiography in the routine assessment of pulmonary haemodynamics. The reason for this may be that Ventricular Mass Index reflects the right ventricular response to a given pulmonary artery pressure sustained over a long period. It is therefore unlikely to be influenced by short-term physiological variables such as heart rate, posture, hydration status or supplementary oxygen, all of which may affect the real-time pressure estimates made by Doppler Echocardiography. Although Doppler Echocardiography is a relatively cheap and practical method of detecting acute disease and assessing acute changes in pulmonary haemodynamics following an intervention such as exercise, Magnetic Resonance Imaging is more likely to provide a reliable assessment of long-term disease progression and response to treatment. This is because ventricular mass is unlikely to respond to transient changes in pulmonary artery pressure.

Magnetic Resonance Imaging does have limitations but was well tolerated by almost all our subjects. The problems of noise, claustrophobia and prolonged breath-holding are fast diminishing with advancing technology. The presence of unsecured ferromagnetic material in the body remains a contraindication. Many patients with pulmonary hypertension are treated with continuous intravenous or subcutaneous prostanoids requiring a syringe pump, which would have to remain outside the scanning room.

There are several possible sources of error in this study. No attempt was made to blind the reporting of scans which may have led to bias and we did not test interobserver reproducibility. Some difficulty was encountered in delineating the right ventricular lumen due to the presence of papillary muscles, in particular at the apex of the ventricle, but this was minimised by adjusting the contrast appropriately. This may have led to a tendency to overestimate right ventricular mass. All our values for left ventricular mass fall within the normal ranges suggested recently by Lorenz et al (119), however only three of our seven subjects without pulmonary hypertension at rest fall within the suggested normal range for right ventricular mass. This may suggest overestimation of right ventricular mass in our study, however we found a similar range of values to Katz et al (122). It should also be remembered that all our "normal" subjects were initially

referred with clinical evidence of pulmonary vascular disease. Since short axis sections for both ventricles were taken perpendicular to the long axis of the left ventricle, this could have led to oblique sections being taken through the right ventricle and inaccuracies in slice volume estimation. Seven of our subjects had ischaemic heart disease or systemic hypertension, possibly altering left ventricular mass and consequently Ventricular Mass Index. However there was no evidence of left ventricular dysfunction or hypertrophy at echocardiography and right heart catheterisation. Although subjects 16,17, 20 and 21 only received supplementary oxygen during Doppler Echocardiography and right heart catheterisation, and not during Magnetic Resonance Imaging, this is unlikely to have affected our anatomical measurements.

We have shown that Magnetic Resonance Imaging may be more accurate than Doppler Echocardiography, with similar or better sensitivity and specificity for both primary and secondary forms of the disease. Although Doppler Echocardiography was successfully performed in almost all subjects in this study, there is known to be a failure rate as high as 60% in some patient groups due to body habitus, the absence of a tricuspid regurgitant jet or co-existing lung disease (78). These are not limiting factors for Magnetic Resonance Imaging which may provide a useful alternative for monitoring patients and screening high risk individuals in whom Doppler Echocardiography is unhelpful. Indeed, with wider availability, reduced costs and the advent of modern scanners it could become the method of choice.

4 Ventricular volumes

4.1 Introduction

Prognosis in pulmonary hypertension (PAHT) depends upon the functional integrity of the right ventricle. Death is commonly due to progressive right heart failure or arrhythmias, however it is unknown why some patients maintain cardiac function while others develop right heart failure in the face of similar pulmonary haemodynamics. Although left ventricular function is compromised (120, 171), the role of the left ventricle in this process is incompletely understood.

The cardiac ventricles are known to respond to sustained rises in afterload by two mechanisms: hypertrophy and dilatation. The former is characterised by raised ventricular mass and the latter by enlarged ventricular volumes. A number of MRI studies have shown that both right ventricular mass (RVM) and right ventricular end-diastolic volume (RVEDV) are raised in PAHT (120, 122, 155, 171, 172), but the factors that determine the extent to which this occurs are unclear. The rise in RVM has been shown to correlate with mean pulmonary artery pressure (MPAP) (122, 172), however a ventricular mass index derived by dividing right by LVM predicts MPAP more accurately than an index derived by dividing by body surface area (BSA) (see Chapter 3) (172). This suggests that left ventricular morphology may also be a factor in determining how the right ventricle responds to pulmonary hypertension, but there have been no published reports of this. Noordegraf et al showed that left ventricular ejection fraction and wall thickness correlated well with right ventricular wall thickness in ten patients with severe emphysema but did not measure pulmonary artery pressure (173). Cardiac output (CO) does not seem to influence RVM (155).

Although the extent of right ventricular dilatation varies widely, there have been no studies showing a relationship between RVEDV and the severity of pulmonary haemodynamics. Boxt et al reported raised RVEDV and reduced left ventricular end-diastolic volume (LVEDV) in eleven patients with primary pulmonary hypertension (PPH) compared to a control group, and proposed that early diastolic paradoxical movement of the left ventricular septum leads to impaired left ventricular filling and

reduced left ventricular stroke volume (120). Marcus et al demonstrated a negative correlation between LVEDV and MPAP in twelve patients with PPH, but did not report a relationship with RVEDV (171). Hoeper et al found no difference in right ventricular volumes between those with a low and a normal CO, although tricuspid regurgitation was more severe in those with a low CO (155).

In this study we used MRI to study the relationship between right ventricular mass and volume, pulmonary haemodynamics and left ventricular mass and volume in patients with a wide range of types of PAHT, in order to better understand the factors that govern right ventricular hypertrophy and dilatation.

4.2 Method

4.2.1 Study subjects

Subjects were recruited as outlined in Chapter 2 and are shown in Table 2C. Twenty-one subjects with pulmonary hypertension were enrolled after informed consent was obtained, however only the sixteen subjects in whom adequate data was obtained were included in the analysis (MPAP 49.6 +/- 15.5 mmHg, CO 4.6 +/- 1.4 L/min). Of these, six had PPH, four connective tissue disease (CTD), three congenital heart disease (CHD), two portopulmonary disease (PP) and one hereditary haemorrhagic telangiectasia (HHT). Images could not be analysed in subjects 16, 18, 19 and 20 due to poor ECG gating, and scanning failed in subject 7 due to acute claustrophobia.

4.2.2 MRI image analysis

MRI scans were performed using a standard scanner (Impact Expert 1.0 T, Siemens Medical Engineering, Erlangen, Germany). Imaging sequences broadly followed the protocol described by Marcus et al (118). Measurements were thought unlikely to be affected by fluctuations in oxygen saturation, and therefore, because of logistical difficulties in supplying oxygen, MRI studies were performed without supplementary oxygen.

RVM and LVM were calculated as described previously (see Chapter 3). RVEDV and LVEDV were calculated as follows: The cross-sectional area of the ventricular lumen in each end-diastolic short-axis slice (Figure 3A) was calculated by manually tracing around the interior margin of the ventricle. The software then calculated the right and left ventricular end-diastolic volume using the same principle as for mass (Chapter 3).

4.2.3 Statistical Analysis

Data was analysed using Minitab for Windows (Release 12.1). Pearson's correlation coefficient and linear regression analysis were used to assess the relationship between variables.

4.3 Results

LVEDV was not obtained in subject 9 due to technical failure. This measurement correlated inversely with MPAP ($r = 0.66$) as has been previously reported (171) but there were no other significant correlations between pulmonary haemodynamics and RVM, RVEDV, LVM and LVEDV (Table 4A). However RVEDV correlated closely with LVM ($r = 0.83$, Figure 4A) even after correcting for BSA ($r = 0.78$, Figure 4B), and RVM correlated with LVM ($r = 0.53$, Figure 4C), even after correction for BSA ($r = 0.54$, Figure 4D).

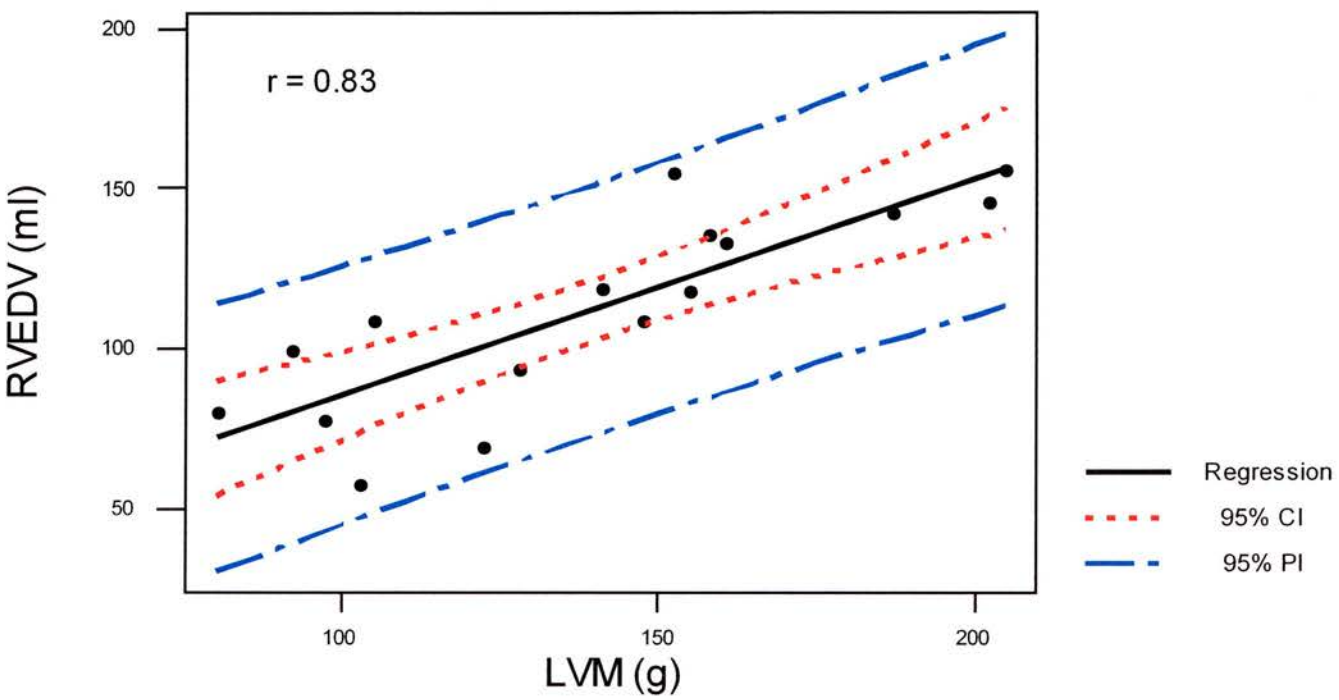
Table 4A: Ventricular volumes and masses with correlations to BSA and pulmonary haemodynamics. Correlations after correction for BSA are shown in parenthesis.

	Mean	±SD	Range	Correlation coefficient (r)		
				BSA	MPAP	CO
RVEDV (mls)	112.0	±31	57.1-155.0	0.59	-0.39 (-0.28)	0.00 (-0.08)
RVM (g)	121.0	±34	62.6-173.9	0.12	0.21 (0.37)	-0.21 (-0.24)
LVEDV (mls)	73.5	±16	51.1-109.1	0.64	-0.66 (-0.63)	0.26 (0.31)
LVM (g)	140.0	±38	80.5-205.0	0.47	-0.38 (-0.24)	0.17 (0.11)

FOOTNOTES:

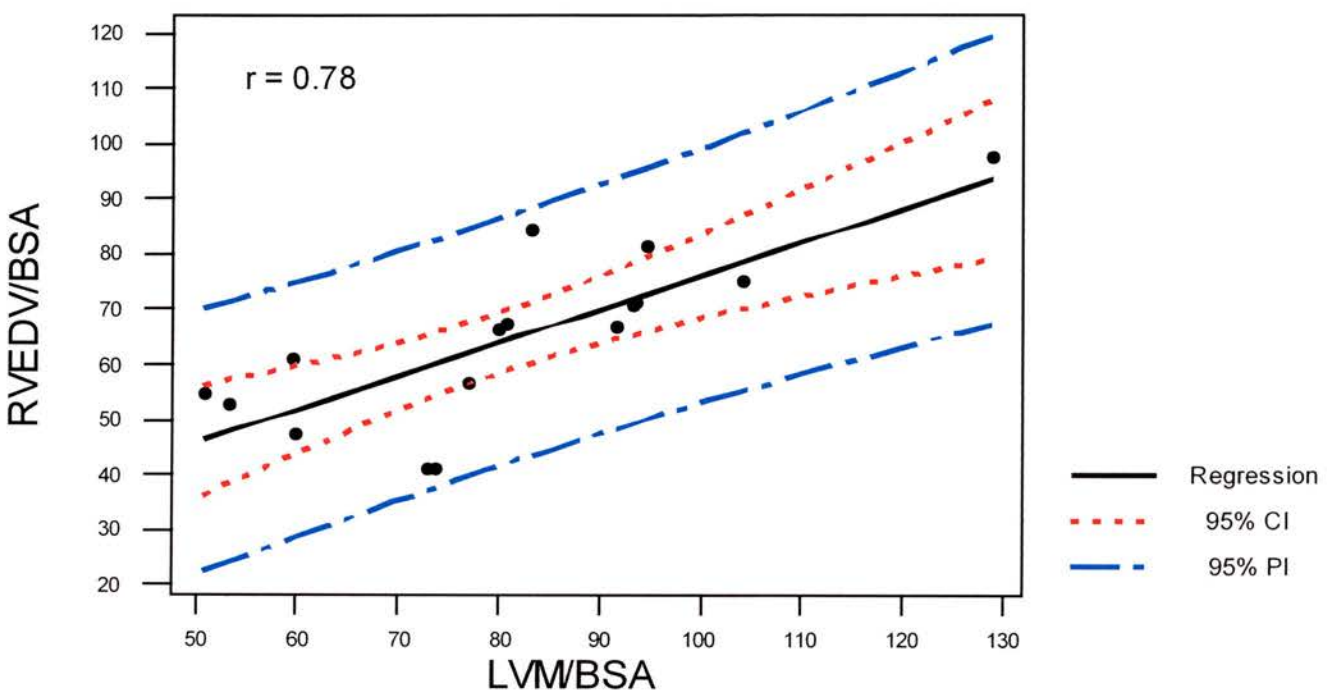
RVEDV = Right ventricular end-diastolic volume, LVEDV = Left ventricular end-diastolic volume, RVM = Right ventricular mass, LVM = Left ventricular mass, BSA = body surface area, MPAP = mean pulmonary artery pressure, CO = Cardiac output, SD = standard deviation

Figure 4A: Correlation between RVEDV and LVM



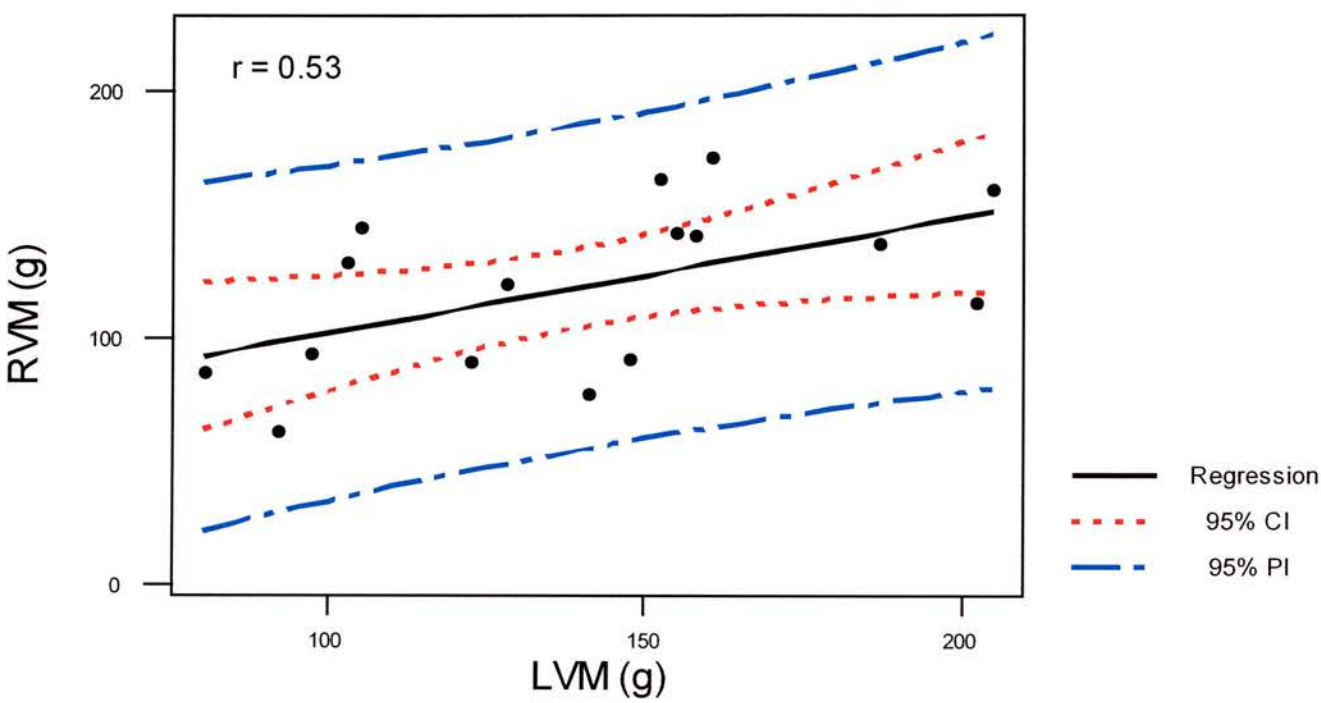
RVEDV = right ventricular end-diastolic volume, LVM = left ventricular mass,
CI = confidence intervals, PI = prediction intervals

Figure 4B: Correlation between RVEDV/BSA and LVM/BSA



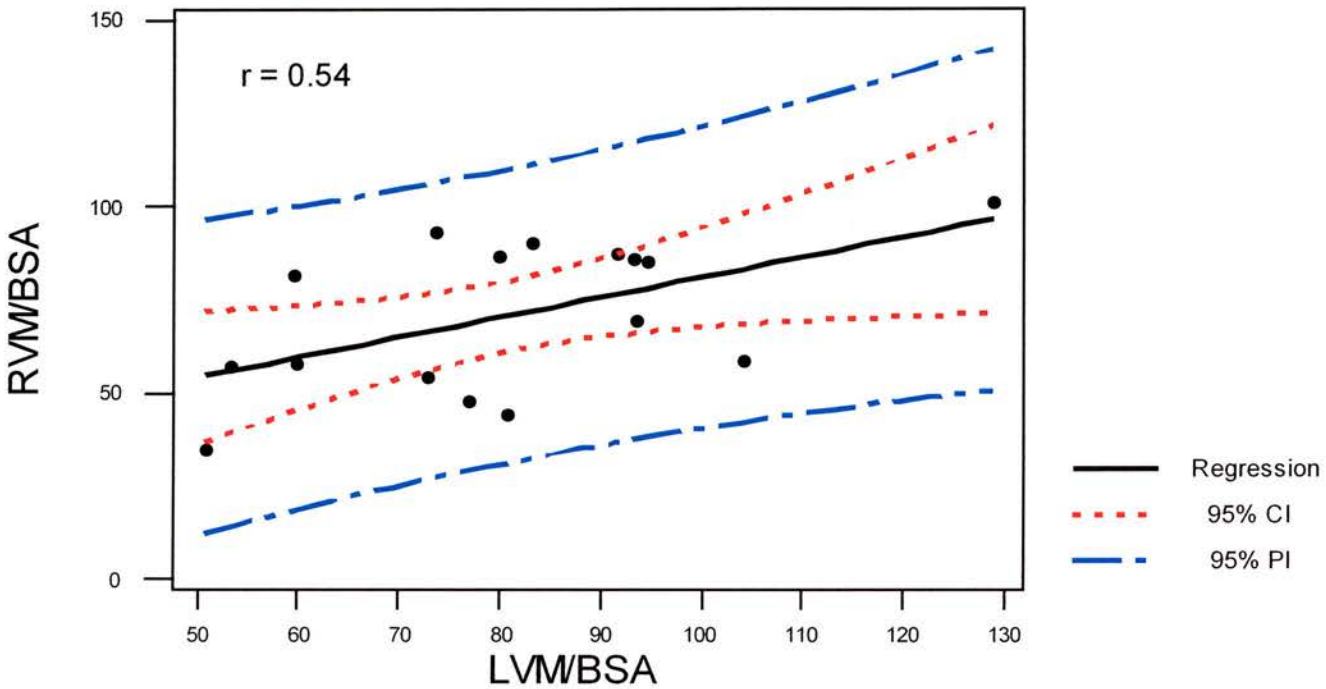
RVEDV = right ventricular end-diastolic volume, LVM = left ventricular mass, BSA = body surface area, CI = confidence intervals, PI = prediction intervals

Figure 4C: Correlation between RVM and LVM



RVM = right ventricular mass, LVM = left ventricular mass, CI = confidence intervals, PI = prediction intervals

Figure 4D: Correlation between RVM/BSA and LVM/BSA



RVM = right ventricular mass, LVM = left ventricular mass, BSA = body surface area, CI = confidence intervals, PI = prediction intervals

4.4 Discussion

In this study, left ventricular mass was more important than pulmonary haemodynamics in determining the right ventricular response to pulmonary hypertension. Right ventricular mass and right ventricular end-diastolic volume correlated closely with left ventricular mass even after correction for body surface area. There was no correlation between left ventricular mass and pulmonary haemodynamics. This observation has not been previously reported and may help us to understand why patients with similar disease severity display widely differing degrees of right ventricular failure and hypertrophy. There are two possible explanations for this. A feature of severe pulmonary hypertension is paradoxical interventricular septal motion, or leftward septal bowing, suggested by Boxt et al as a cause of impaired left ventricular filling (120). Increased left ventricular mass is likely to result in reduced ventricular compliance. This may provide a survival advantage by splinting the left ventricular cavity and limiting collapse of the left ventricle during diastole, allowing the heart to tolerate greater degrees of right ventricular hypertrophy and dilatation. Patients with smaller left ventricular muscle mass may die earlier in the course of the disease. This may also explain the observed association between pulmonary hypertension and systemic hypertension (174), since the resultant left ventricular hypertrophy may be protective. A second possibility is that the left ventricle may hypertrophy in response to recurrent encroachment by the right ventricle and persistently low cardiac output, or some other mechanical or endocrine stimulus. This is consistent with earlier studies that have clearly shown that left ventricular hypertrophy occurs in animal models of pulmonary hypertension (175, 176). Laks et al suggested that the ventricles may behave as a single structure and that sustained overload of one could result in hypertrophy and dilatation of both (175). Our values for left ventricular mass fall within the normal ranges recently suggested by Lorenz et al (119), although values for three female subjects were more than one standard deviation above the mean. Two subjects had controlled systemic hypertension (subjects 1 and 8) and one ischaemic heart disease (subject 16), but there was no clear evidence of left ventricular hypertrophy or dysfunction at echocardiography or right heart catheterisation in any of these patients.

In healthy individuals, there is a linear relationship between body surface area and right ventricular mass and end-diastolic volume (119). We expected this relationship to be overwhelmed in pulmonary hypertension, with right ventricular parameters being dictated primarily by pulmonary haemodynamics. This was indeed the case in our study for mass, but not for volume. For similar reasons, we did not expect to find such a strong relationship between right and left ventricular mass. We also expected right ventricular mass, and perhaps end-diastolic volume, to correlate with the severity of disordered pulmonary haemodynamics, but this was not the case for either in our study. Some studies (122) have reported a correlation between right ventricular mass and mean pulmonary artery pressure whereas others did not find one (155). There have been no studies relating right ventricular end-diastolic volume to pulmonary haemodynamics. Boxt et al did not report any correlations in a study of eleven patients with primary pulmonary hypertension (120). Hoeper et al found no difference in right ventricular end-diastolic volume and mass between two groups of patients with "normal" and "low" cardiac outputs (155).

It is becoming clear that a number of additional factors are involved in the right ventricular response to pulmonary hypertension. The extent of right ventricular dilatation appears to depend upon left ventricular mass and body surface area. The extent of right ventricular hypertrophy appears to depend upon both mean pulmonary artery pressure and left ventricular mass, which may explain the accuracy of a ventricular mass index derived by dividing right ventricular mass by left ventricular mass at predicting mean pulmonary artery pressure (172).

This study was limited by the fact that all of our subjects were known to have abnormal right ventricular function and morphology at echocardiography, with the exception of subject 22 who was diagnosed at elective right heart catheterisation during liver transplantation. This is inevitable since the vast majority of patients are picked up on the basis of abnormalities at echocardiography. Unfortunately this deprives us of the chance to study patients in the early stages of disease, before the right ventricle becomes abnormal. Earlier detection of disease is needed to make these important studies possible.

There are a number of potential sources of error in our study. No attempt was made to blind the reporting of scans which may have led to bias and we did not test interobserver

reproducibility. Since short axis sections for both ventricles were taken perpendicular to the long axis of the left ventricle, this could have led to oblique sections being taken through the right ventricle and inaccuracies in slice volume estimation. Some difficulty was encountered in delineating the right ventricular lumen due to the presence of papillary muscles, in particular at the apex of the ventricle, but this was minimised by adjusting the contrast appropriately. This may have led to a tendency to overestimate right ventricular mass and underestimate right ventricular end-diastolic volume, however previous studies have reported similar values for mass (122) and volume (120) in pulmonary hypertension. Furthermore, any error is likely to be systematic and should not affect correlations between variables. Although subjects 17 and 21 only received supplementary oxygen during right heart catheterisation, and not during Magnetic Resonance Imaging, this is unlikely to have affected our anatomical measurements.

In summary, this study has shown that increased left ventricular mass correlates better with right ventricular hypertrophy and dilatation than pulmonary haemodynamics. This may be because increased left ventricular mass leads to reduced compliance and splinting of the left ventricle. This in turn may provide a survival advantage by preventing the impaired left ventricular filling seen in severe pulmonary hypertension. Alternatively, right ventricular overload may result in left ventricular hypertrophy.

5 Ventricular wall thickness

5.1 Introduction

Pulmonary hypertension is characterised by right ventricular dilatation and hypertrophy. The increase in right ventricular mass correlates well with the rise in pulmonary artery pressure, especially after correcting for body habitus (122, 172). Although this can be used to detect and quantify pulmonary hypertension (see Chapter 3), it is time consuming and cumbersome. A number of investigators have proposed measuring right ventricular wall thickness (RVWT) instead, and several echocardiographic and MRI studies have been published using a variety of approaches. Subxiphoid echocardiography has been used to quantify right ventricular hypertrophy (177) and a correlation has been reported with MPAP and total pulmonary resistance in thirty-three subjects with sarcoidosis (178). Tsuda et al used three different echocardiographic approaches to study twenty-one subjects with right ventricular overload due to a variety of congenital and acquired cardiac disorders and found a good correlation with systolic PAP (179).

MRI has three important advantages over echocardiography in measuring RVWT. Firstly, it can provide cross-sectional images in any plane allowing measurements to be made at right angles to the ventricular wall. Secondly, these measurements can be made in several places if required, and thirdly it gives superb discrimination between blood, fat and muscle and anatomical measurements are accurate and reproducible (see Chapter 3). In 1985, Longmore et al reported close agreement between direct and MRI measurements of right ventricular wall thickness in a study using a porcine heart model (180). Since then, a number of studies have shown increased RVWT to be a marker of raised PAP (123, 125, 136, 181, 182). Three of these studies reported correlations with MPAP, two using measurements of the right ventricular free wall (125, 136) and the third using measurements in the right ventricular outflow tract (123). In addition, an attempt was made to correct for body habitus by some investigators using body surface area (BSA) (125) or LVPWT (136) but not in others. There have been no studies comparing the accuracy of RVWT and doppler echocardiography in predicting pulmonary artery pressure.

The purpose of this study was to see if a single simple MRI measurement of RVWT would accurately predict MPAP at routine cardiac catheterisation in subjects referred for investigation or reassessment of pulmonary hypertension. We then made a comparison with doppler echocardiography, the current non-invasive gold standard.

5.2 Method

5.2.1 Study subjects

Subjects were recruited as outlined in Chapter 2 and are shown in Table 2C. Subjects 27 and 28 were not included in this study because the interval between RHC and Echo of four weeks was considered to be too long to make an accurate comparison.

5.2.2 MRI image analysis

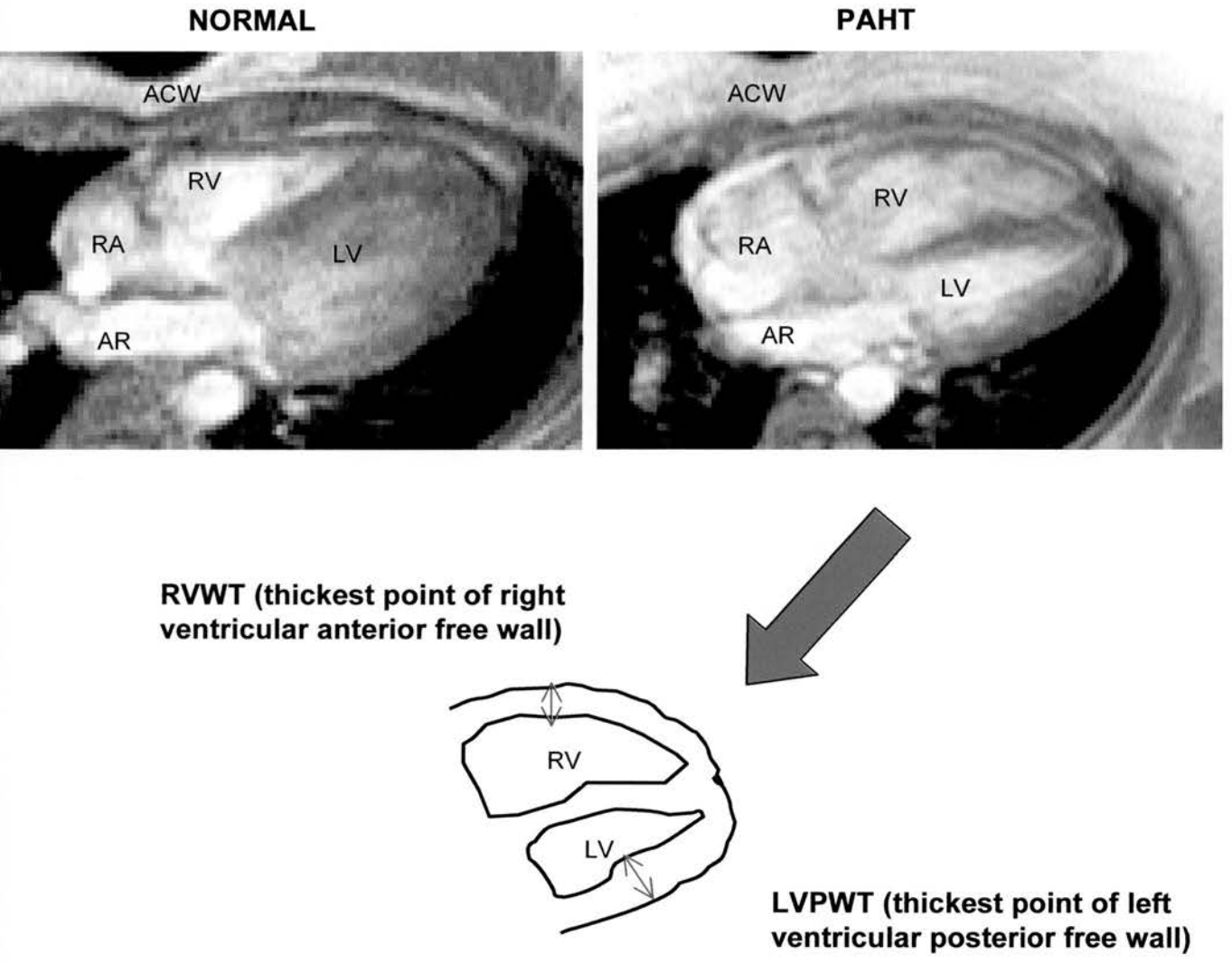
RVWT was defined as the thickest part of the right ventricular free wall measured in millimetres between base and apex seen on the end-diastolic four-chamber long-axis view (Figure 5A). Similarly, LVPWT was defined as the thickest part of the free left ventricular wall on the same image. LVM was calculated using the method described in Chapter 3.

Three forms of RVWT index were calculated by dividing RVWT by BSA, LVPWT and LVM in turn.

5.2.3 Statistical analysis

Data was analysed using Minitab for Windows (Release 12.1). Pearson's correlation coefficient and linear regression analysis were used to assess the relationship between MPAP measured at RHC and measurements made at Echo and MRI. Subjects were also divided into those with normal MPAP at RHC (Normals) and those with raised MPAP

Figure 5A: Four chamber images used to measure RVWT and LVPWT



RVWT = right ventricular wall thickness, LVPWT = left ventricular posterior wall thickness, ACW = anterior chest wall, RA = right atrium, RV = right ventricle, LV = left ventricle, AR = aortic root

(PAHT). The 2 sample t test was used to assess the significance of differences between the two groups. An "intention to scan" analysis was done when calculating sensitivities and specificities.

5.3 Results

5.3.1 RVWT, LVPWT and LVM

RVWT was successfully measured in twenty-five subjects, LVPWT in twenty-three and LVM in twenty-four. Scanning was incomplete in subject 7 due to claustrophobia and subjects 16 and 18 due to breathlessness. There was a significant difference between the two groups for RVWT ($p<0.0001$) but not for LVPWT or LVM (Table 5A). There was also a close correlation between RVWT and MPAP ($r = 0.83$, Figure 5B). If we take a RVWT of 8 millimetres as abnormal then there is one false negative and no false positives and one failed scan giving a sensitivity of 89% and a specificity of 100% (Table 5B).

5.3.2 RVWT indices

All three indices of RVWT successfully distinguished between the Normal and PAHT groups (Table 5A), however none improved correlation or accuracy. Indexing with BSA yielded a similar correlation with the same degree of scatter (Figure 5C). Accuracy actually deteriorated after indexing with LVPWT and LVM with the majority of points on the graph lying to one side and the apparently good correlations dependent upon a few outlying points (Figures 5D and 5E).

5.3.3 Doppler Echocardiography

The values for estimated PASP are shown in Table 3A and statistical analysis in Tables 5A and 5B. Values are listed for twenty-four subjects; subject 6 was reported as " < 25 " and a value of 25 was used for statistical analysis. In subject 8, estimated PASP was

raised but could not be accurately measured, and was therefore not included in linear regression analysis. PASP could not be measured in subject 22. There was a significant difference between the two groups ($p < 0.0001$) and a good correlation with MPAP as shown in Figure 3E ($r = 0.77$). However there were three false positive results (subjects 4,11 and 25), one failed scan (subject 22) and one false negative result (subject 13), giving an overall sensitivity of 89% and a specificity of 57% (Table 5B).

Table 5A: Comparison : Normals vs PAHT

	NORMALS (n=7)		PAHT (n=19)		
	Mean ±SD	Range	Mean ±SD	Range	p-value
AGE (yrs)	50 ± 11	32-64	50 ± 12	29-68	NS
MPAP (mmHg)	17 ± 2	15-19	47 ± 16	27-78	< 0.0001
CO (L/min)	5.1 ± 1.2	3.4-6.8	4.4 ± 1.3	2.6-6.7	NS
RVWT (mm)	6 ± 2	4 - 9	13 ± 4	6 - 21	< 0.0001
LVPWT (mm)	13 ± 3	8 - 16	15 ± 3	10- 23	NS (0.16)
LVM (g)	129 ±24	98-172	145 ± 41	81-205	NS
RVWT/BSA	3.7 ± 0.9	2.2 – 4.6	7.6 ± 2.9	3.1 – 15.0	< 0.0001
RVWT/LVPWT	0.5 ± 0.1	0.3 – 0.6	0.9 ± 0.3	0.4 – 1.9	0.0003
RVWT/LVM	0.049 ± 0.015	0.031 – 0.071	0.099 ± 0.049	0.041 – 0.204	0.0009
Echo PASP (mmHg)	31 ± 11	16-49	75 ± 33	25-144	< 0.0001

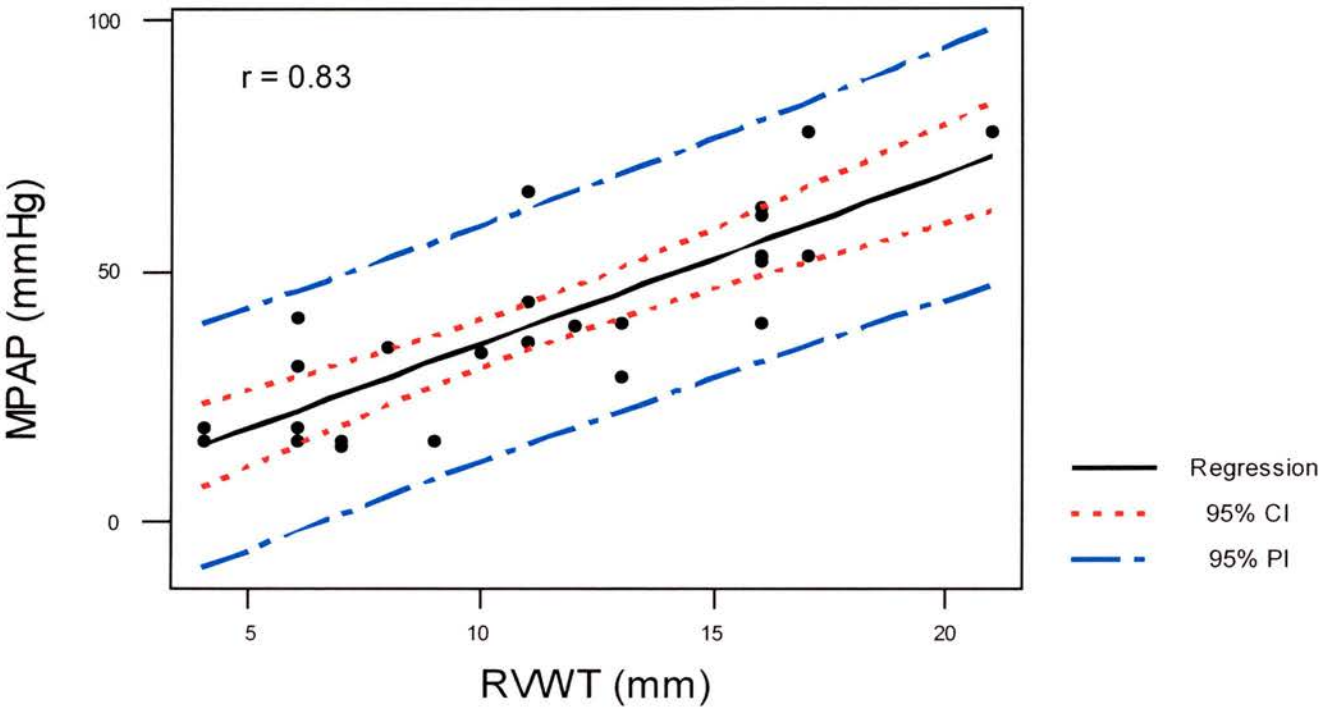
Table 5B: Correlations with MPAP and sensitivity and specificity for PAHT

		Correlation with MPAP	Sensitivity for PAHT	Specificity for PAHT
RVWT (mm)	(n = 26)	r = 0.83	89%	100%
Echo PASP (mmHg)	(n = 26)	r = 0.77	89 %	57 %

FOOTNOTES:

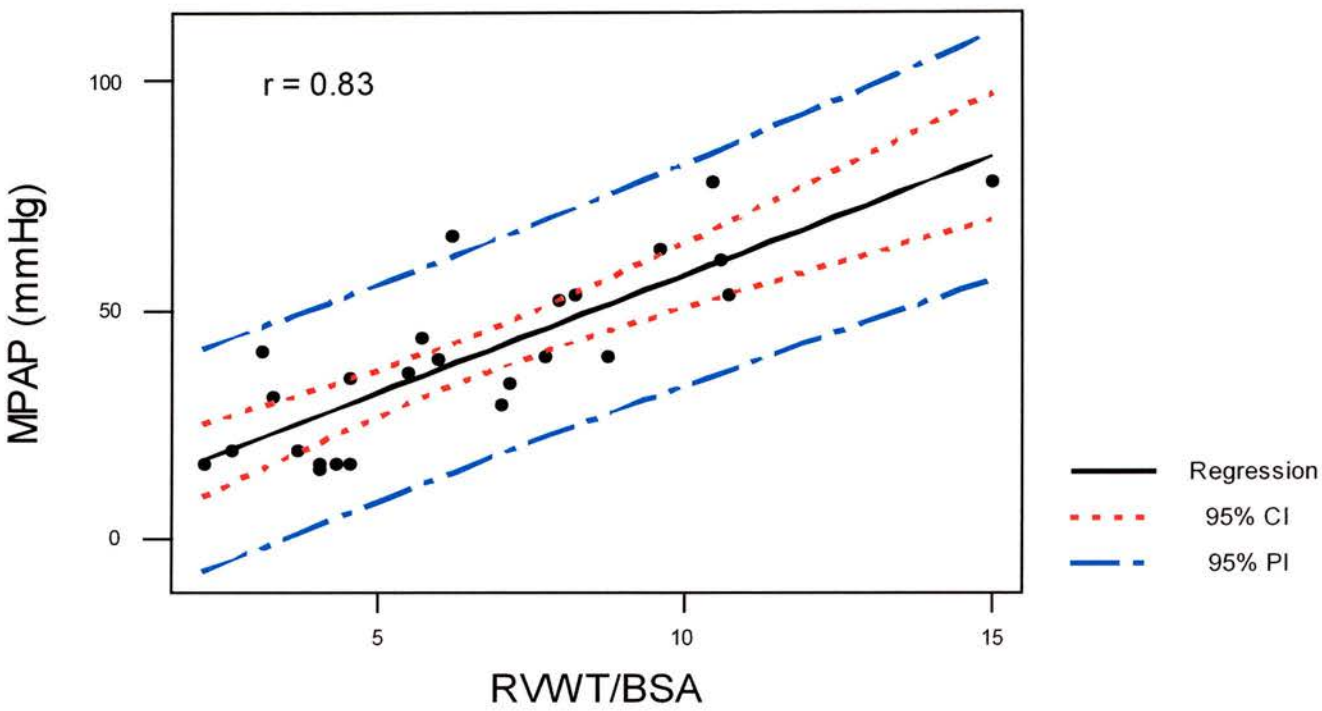
PAHT = pulmonary arterial hypertension, BSA = body surface area, MPAP = mean pulmonary artery pressure, CO = Cardiac output, RVWT = right ventricular wall thickness, LVPWT = left ventricular posterior wall thickness, LVM = left ventricular mass, Echo = Doppler echocardiography, PASP = pulmonary artery systolic pressure, SD = Standard deviation, NS = Not significant.

Figure 5B: Correlation between MPAP and RVWT



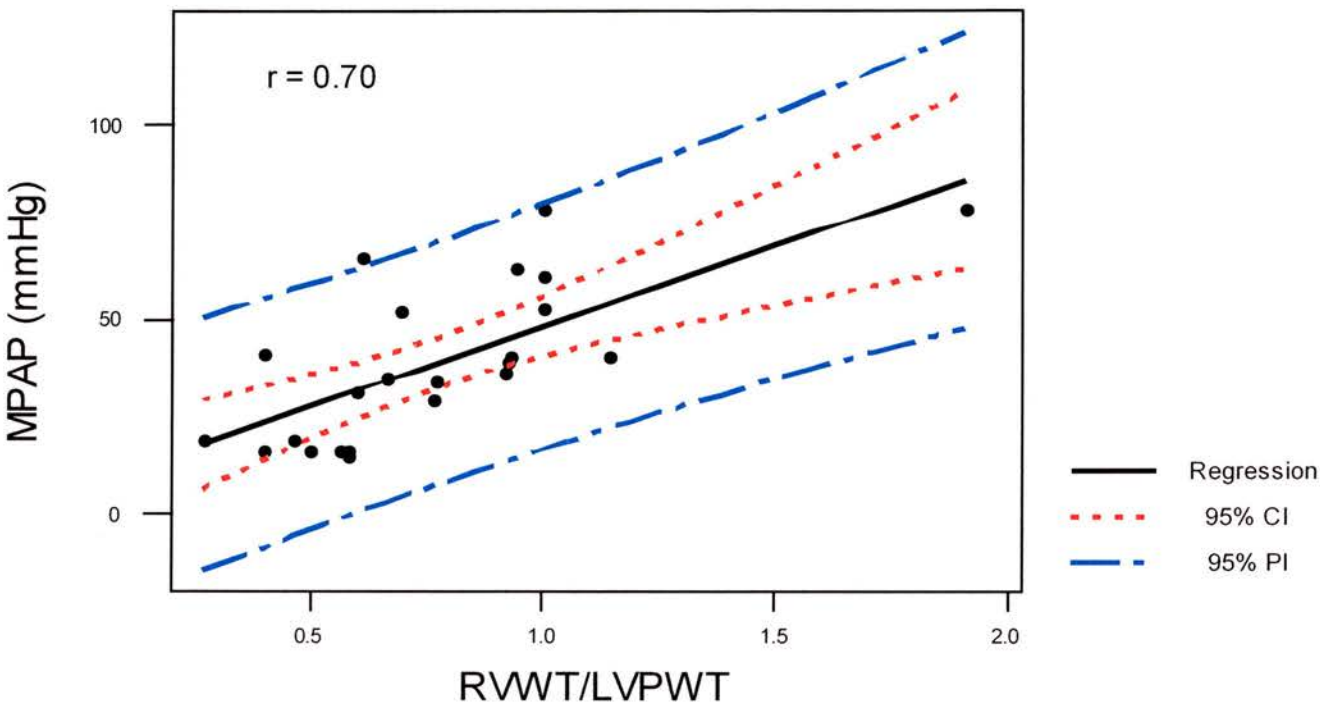
MPAP = mean pulmonary artery pressure, RVWT = right ventricular wall thickness,
CI = confidence intervals, PI = prediction intervals

Figure 5C: Correlation between MPAP and RVWT/BSA



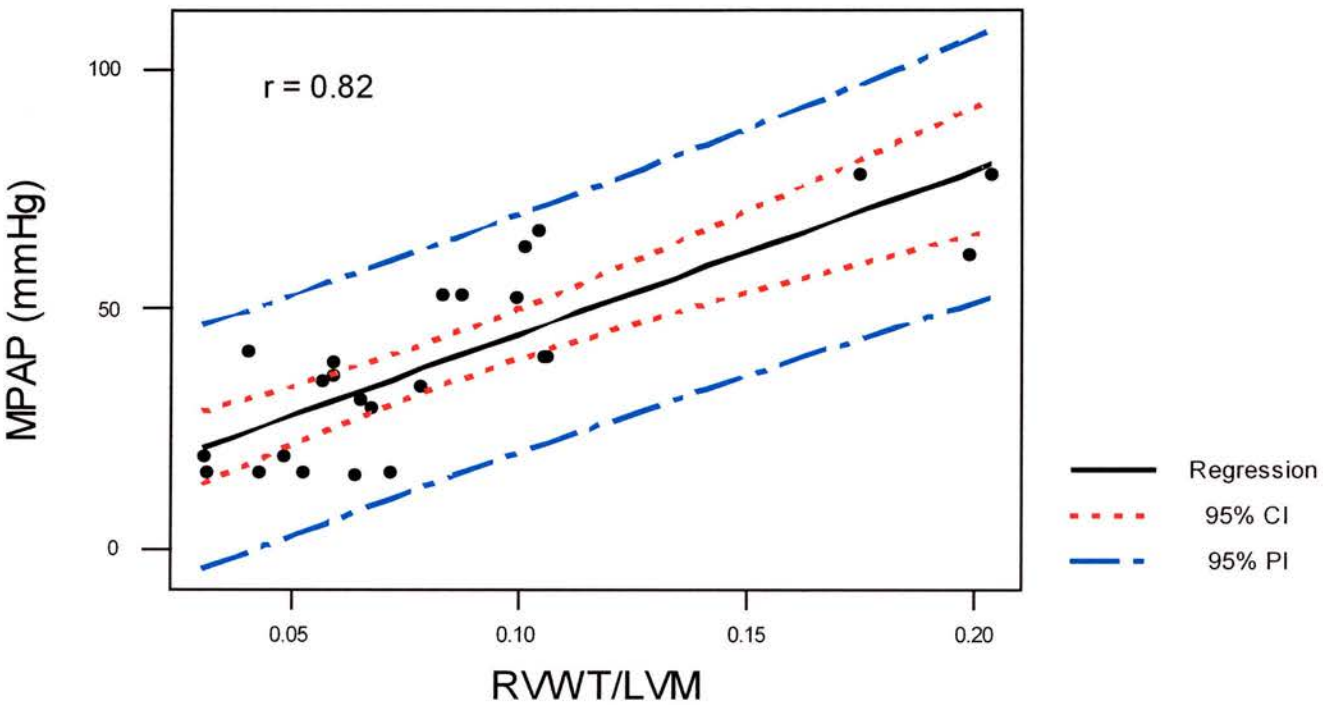
MPAP = mean pulmonary artery pressure, RVWT = right ventricular wall thickness, BSA = body surface area, CI = confidence intervals, PI = prediction intervals

Figure 5D: Correlation between MPAP and RVWT/LVPWT



MPAP = mean pulmonary artery pressure, RVWT = right ventricular wall thickness,
LVPWT = left ventricular posterior wall thickness, CI = confidence intervals, PI = prediction intervals

Figure 5E: Correlation between MPAP and RVWT/LVM



MPAP = mean pulmonary artery pressure, RVWT = right ventricular wall thickness, LVM = left ventricular mass, CI = confidence intervals, PI = prediction intervals

5.4 Discussion

This study has shown that a single simple MRI measurement of right ventricular wall thickness predicts mean pulmonary artery pressure with similar accuracy and sensitivity, but better specificity than doppler echocardiography in primary and secondary pulmonary hypertension. This may be because echocardiography is confounded by the known spontaneous variability in pulmonary haemodynamics (108). Correcting for body habitus by indexing for body surface area, left ventricular posterior wall thickness or left ventricular mass did not improve the correlation and may be unnecessary.

Our results are similar to those previously reported using a variety of end-diastolic methods (123, 125, 136). Saito et al chose to make their measurements on a modified short axis section immediately under the right ventricular outflow tract, an area relatively free from trabeculation (136). Frank et al measured wall thickness at the mid-ventricular free wall on a four chamber view similar to that used in this study (125). Bouchard used a calibrated grid method in the right ventricular outflow tract on a transverse section of the heart (123, 183). We chose to make our measurements at the thickest point on a long-axis view of the ventricle in an attempt to standardise the technique and make it less subjective while keeping it simple and practical. We used body surface area and left ventricular parameters to index our measurement as suggested by the literature and our own work (Chapters 3 and 4)(172).

The normal right ventricle is a surprisingly thin walled structure. Pathological studies estimate the normal right ventricular free wall to be about 2-4 mm thick (184). Echocardiographic studies have reported a value of between 2 and 5 mm (177-179), depending upon the approach and technique employed. MRI studies have been very consistent irrespective of technique: Markiewicz reported the normal range to be 2.9 ±0.9 mm in twenty five controls (181). Frank et al found values of 2-3 mm in eight controls (125). Suzuki et al studied nine healthy volunteers and found normal values to be 2.9 ±0.8 mm (182) and Bouchard et al reported normal values of 3 ±1 mm in ten controls (123). Our normal values were significantly higher than this. The most likely explanation of this discrepancy is that, unlike previous investigators, we defined RVWT as being the *thickest* part of the right ventricular free wall. Another possible explanation is that our

"normals" were not true matched controls. All had been referred with a strong clinical suspicion of pulmonary vascular disease, however its worth noting that our RVWT values for those with PAHT are also higher than those reported.

It is not entirely surprising that measurements of right ventricular wall thickness predict mean pulmonary artery pressure irrespective of the method used, because the right ventricle functions as a unit and the excess load is likely to be evenly distributed. What is unexpected is the degree of accuracy derived from single measurements of wall thickness even without correction for body habitus, when more variation would be expected due to oblique positioning of the scan and the inherent irregularity of the wall. Wall thickness appears to be more accurate than uncorrected mass measurements (122, 172). Furthermore, we know from pathological studies that right ventricular wall thickness correlates poorly with ventricular weight (185, 186). This suggests that right ventricular wall thickness does not depend upon body habitus and simply reflects the work of the right ventricle. It may therefore prove to be a reliable and accurate way of detecting pulmonary hypertension and monitoring the response to treatment. There is already echocardiographic and MRI evidence of significant reduction in right ventricular wall thickness within 3-12 months of single lung transplantation (129, 187) and further studies are needed of the long term effects of medical therapy.

So how should this measurement be made? As described earlier, MRI has several advantages over doppler echocardiography and this study has highlighted a further important advantage. Echocardiography has a reported success rate of between 50% and 90% in measuring RVWT, depending upon the approach employed and the operator (177, 179). Tsuda et al compared three techniques and reported the best to be an anterior approach in the supine position with a success rate of only 80% (179). In contrast, we successfully studied twenty-five out of twenty-six subjects: our only failure suffered from acute claustrophobia (subject 7). There were no failures reported in any of the earlier studies.

There are a number of possible sources of error in this study. No attempt was made to blind the reporting of scans which may have led to bias, and we did not test inter and intra-observer reproducibility. Although every effort was made to make measurements in a plane orthogonal to the right ventricular free wall, some images may have been oblique

leading to higher values. Seven of our subjects had ischaemic heart disease or systemic hypertension, possibly altering left ventricular mass and posterior wall thickness. However there was no evidence of left ventricular dysfunction or hypertrophy at echocardiography and right heart catheterisation. Although subjects 16,17,20 and 21 only received supplementary oxygen during Doppler Echocardiography and right heart catheterisation, and not during Magnetic Resonance Imaging, this is unlikely to have affected our anatomical measurements.

In summary, this study has shown that a single simple unindexed measurement of right ventricular wall thickness predicts mean pulmonary artery pressure with similar accuracy and better specificity than conventional doppler echocardiography of the tricuspid valve in pulmonary hypertension.

6 Measurements of great vessels

6.1 Introduction

Computerised axial tomography (CT) and Magnetic resonance imaging (MRI) can be used to make accurate measurements of the great vessels and dilatation of the main pulmonary artery has been shown to be a marker for the presence of raised pressure (123-125, 139-141, 188-190). In 1998 Edwards et al reported that the upper limit of normal for main pulmonary artery diameter (MPAD) was 33.2 mm after a study of one hundred normal subjects and twelve patients with PAHT (190). A number of studies have used MPAD as a non-invasive method of estimating MPAP with some reporting significant correlations (123, 125, 139-141) and others not (124, 188, 189), however there have been no direct comparisons with Echo. The ratio of MPAD to aortic diameter (AOD) has also been shown to correlate with MPAP (123, 124). In a recent study, Ng et al retrospectively reviewed the CT scans of fifty patients with a wide range of pulmonary and cardiac diseases who had also undergone cardiac catheterisation and suggested the finding "MPAD/AOD > 1" as an accurate sign of the presence of PAHT (139).

In this study we set out to test the accuracy of MRI measurements of the main pulmonary artery and aorta in detecting and quantifying raised MPAP, using the normal limits proposed by Edwards et al (190) and the ratio suggested by Ng et al (139). We prospectively studied a heterogeneous group of patients referred to our centre for investigation of suspected pulmonary hypertension. We then determined whether adjusting for body surface area improved predictive accuracy. Finally, we made a comparison with doppler echocardiography.

6.2 Method

6.2.1 Study subjects

Subjects were recruited as outlined in Chapter 2 and are shown in Table 2C. Subjects 27 and 28 were not included in this study because the interval between RHC and Echo of

four weeks was considered to be too long to make an accurate comparison. Twenty-six subjects were enrolled after informed consent was obtained. All had normal left ventricular function and morphology at echocardiography. PAHT was defined as MPAP of 25 mmHg or more (5).

PAHT was confirmed in nineteen subjects, of whom six had PPH, four connective tissue disease (CTD), three congenital heart disease (CHD), two chronic obstructive pulmonary disease (COPD), two portopulmonary disease (PP), one chronic thromboemboembolism (CTEPHT) and one hereditary haemorrhagic telangiectasia (HHT). The remaining seven had normal pulmonary haemodynamics at cardiac catheterisation, and had been referred because of evidence of PAHT at Echo (subjects 4,6,11,12,25) or cardiopulmonary exercise testing (subjects 14,23).

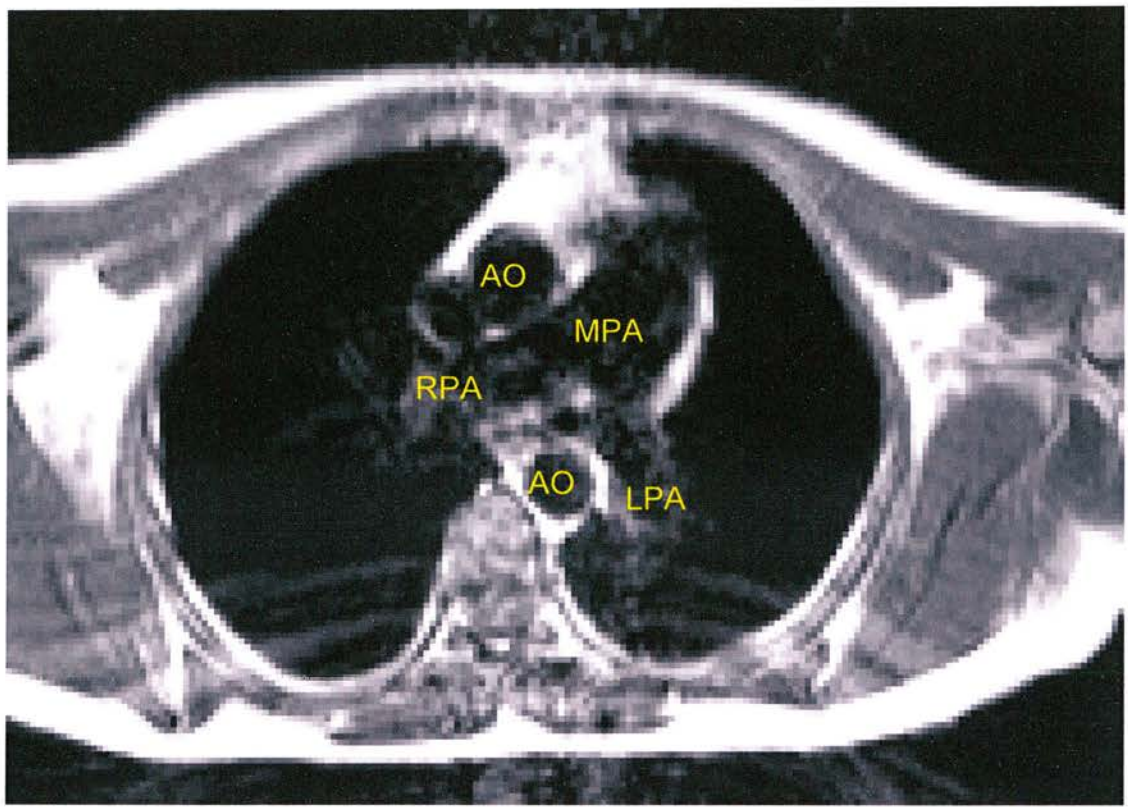
6.2.2 MRI Image Analysis

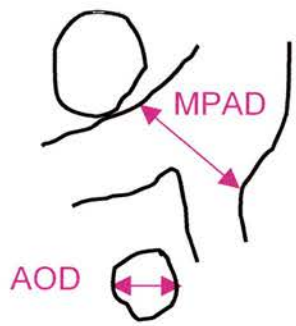
MPAD was taken as the largest internal diameter in millimetres of the main pulmonary artery before bifurcation (Figure 6A). The image showing the largest MPAD was used for analysis. AO was taken as the largest internal diameter in millimetres of the descending aorta on the same image (Figure 6A). MPAD was adjusted for body size by dividing by body surface area.

6.2.3 Statistical Analysis

Data was analysed using Minitab for Windows (Release 12.1). Pearson's correlation coefficient and linear regression analysis were used to assess the relationship between MPAP measured at cardiac catheterisation and measurements made at Echo and MRI. Sensitivities, specificities, positive and negative predictive values were calculated. An "intention to scan" analysis was done when calculating sensitivities and specificities.

Figure 6A: Cross-sectional images used to measure MPAD and AOD





MPAD = main pulmonary artery diameter, AOD = diameter of descending aorta, AO = aorta, MPA = main pulmonary artery, RPA = right pulmonary artery, LPA = left pulmonary artery

6.3 Results

6.3.1 General

Twenty out of twenty-six subjects underwent MRI within two days of cardiac catheterisation. The remaining six were scanned within two weeks (subjects 1,2,6,15,19 and 21). Measurements were successfully obtained in twenty-five subjects, but scanning was abandoned in one subject due to claustrophobia (subject 7). All twenty-six subjects underwent Echo within two days of cardiac catheterisation, however values are only available for twenty-four subjects; in subject 8 PASP was raised but could not be accurately measured, and was therefore not included in linear regression analysis; in subject 22 PASP could not be measured. In subject 6 PASP was reported as " < 25 " and a value of 25 was used for statistical analysis. Echo and cardiac catheter measurements are shown in Table 2C with correlations in Table 6A. Raw MRI data is shown in Appendix 2. Sensitivities, specificities, positive and negative predictive values are shown in Table 6B.

Table 6A: Correlations of MRI and Echo measurements with MPAP

	r value	p value
MPAD	0.62	0.001
MPAD/BSA	0.71	<0.001
MPAD/AOD	0.82	<0.001
Echo PASP	0.77	<0.001

FOOTNOTES:

MPAD = Main pulmonary artery diameter, AOD = Diameter of descending aorta, BSA = body surface area, Echo = Doppler echocardiography, PASP = pulmonary artery systolic pressure

Table 6B: Sensitivities, specificities, positive and negative predictive values for MRI and Echo measurements

	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %
MPAD	79	100	100	70
MPAD/BSA	89	86	94	86
MPAD/AOD	95	57	86	100
Echo PASP	89	57	85	80

(Using MPAD > 33.2mm, MPAD/BSA > 16, MPAD/AOD > 1 and Echo PASP > 35mmHg as indicative of pulmonary arterial hypertension)

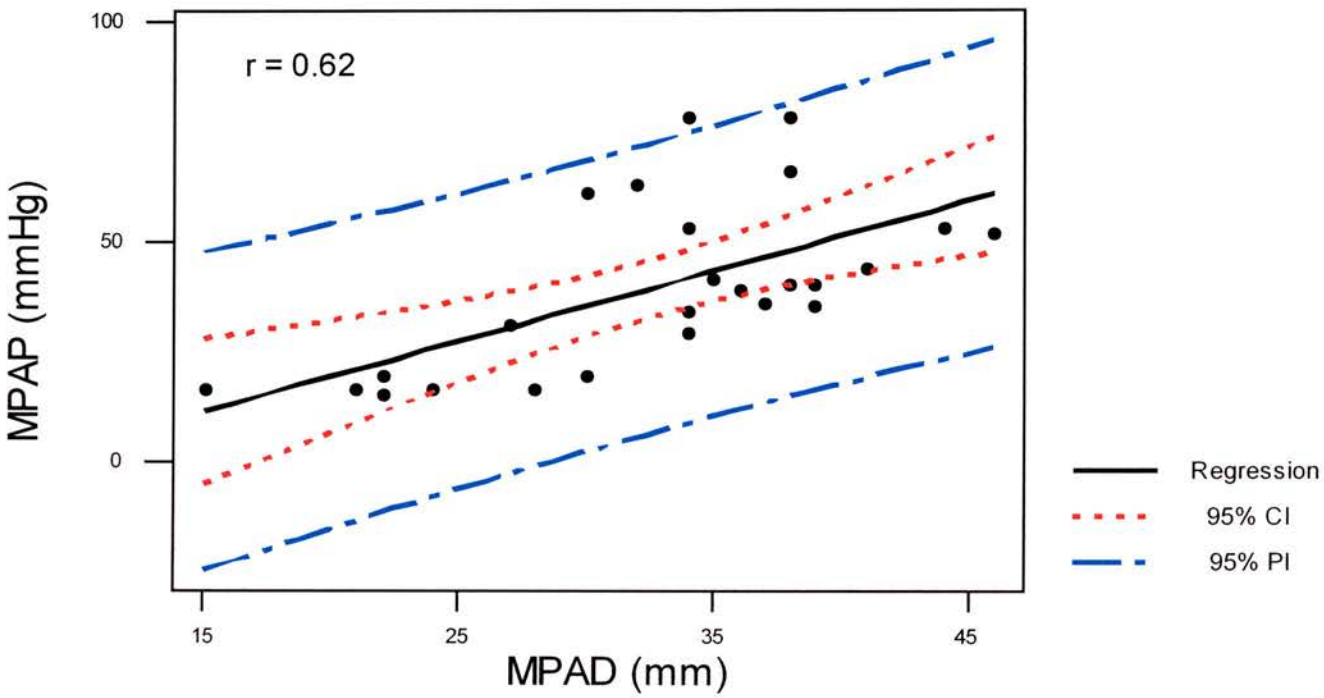
FOOTNOTES:

MPAD = Main pulmonary artery diameter, AOD = Diameter of descending aorta, BSA = body surface area, Echo = Doppler echocardiography, PASP = pulmonary artery systolic pressure

6.3.2 Quantification of pulmonary artery pressure

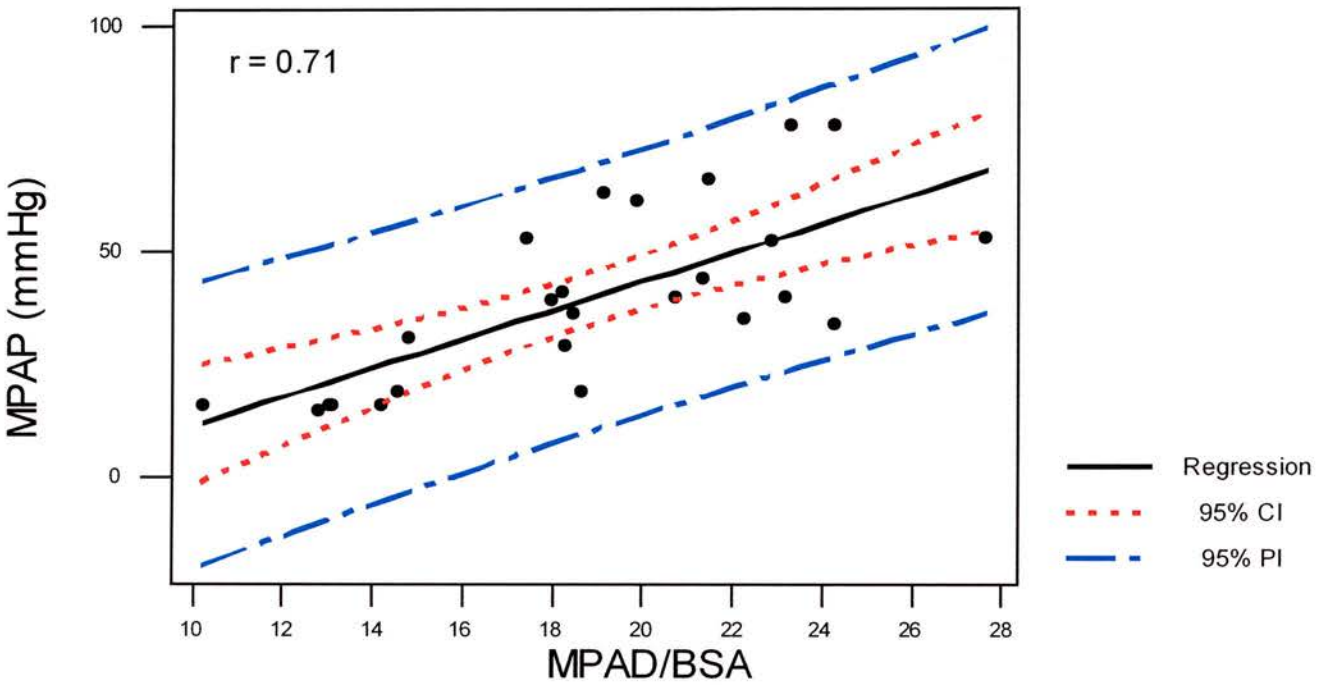
There was a significant correlation between MPAP and MPAD (r = 0.62, Figure 6B), with a small improvement after adjusting for differences in body size (r = 0.71, Figure 6C). The closest correlation obtained was between MPAP and MPAD/AOD (r = 0.82, Figure 6D). Agreement with Echo was less good with more scatter and wider confidence intervals (r = 0.77, Figure 3E).

Figure 6B: Correlation between MPAP and MPAD



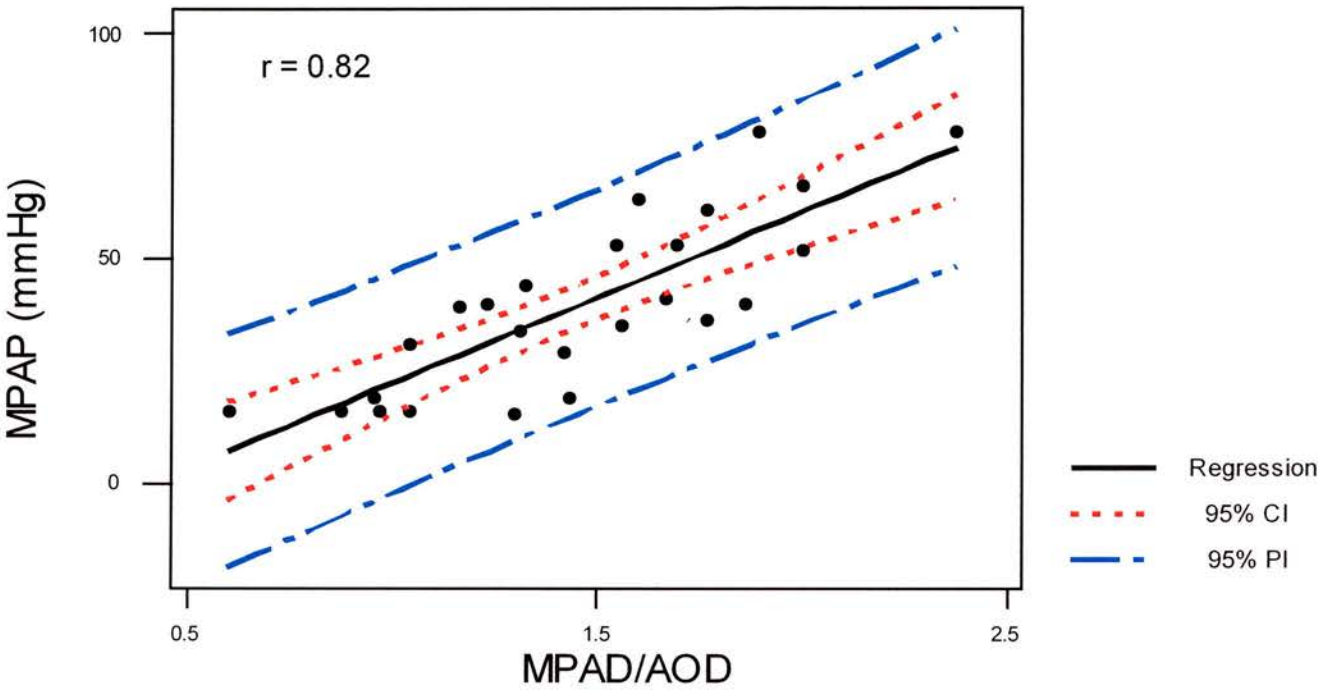
MPAP = mean pulmonary artery pressure, MPAD = main pulmonary artery diameter, CI = confidence intervals, PI = prediction intervals

Figure 6C: Correlation between MPAP and MPAD/BSA



MPAP = mean pulmonary artery pressure, MPAD = main pulmonary artery diameter, BSA = body surface area, CI = confidence intervals, PI = prediction intervals

Figure 6D: Correlation between MPAP and MPAD/AOD



MPAP = mean pulmonary artery pressure, MPAD = main pulmonary artery diameter, AOD = diameter of descending aorta, CI = confidence intervals, PI = prediction intervals

6.3.3 Detection of pulmonary hypertension

6.3.3.1 MPAD

If we take values of MPAD above 33.2 mm as abnormal then there would be no false positives, three false negatives (subjects 2,5,13) and one failed scan, giving sensitivity 79%, specificity 100%, positive predictive value 100% (15/15) and negative predictive value 70% (7/10)(Table 6B).

6.3.3.2 MPAD/BSA

If we take values of MPAD/BSA above 16 as indicative of PAHT then there would only be one false positive (subject 6), one false negative (subject 13) and one failed scan, giving sensitivity 89%, specificity 86%, positive predictive value 94% (17/18) and negative predictive value 86% (6/7).

6.3.3.3 MPAD/AOD

If we take a MPAD/AOD ratio of > 1 to be abnormal then there are three false positives (subjects 6,11,23), no false negatives and one failed scan, giving sensitivity 95%, specificity 57%, positive predictive value 86% (18/21) and negative predictive value 100% (4/4) respectively.

6.3.3.4 Echo PASP

Taking a pressure of > 35 mmHg as abnormal, there were three false positives (subjects 4,11 and 25), one false negative (subject 13) and one failed scan (subject 22) giving overall sensitivity 89%, specificity of 57%, positive predictive value 85% (17/20) and negative predictive value 80% (4/5).

6.4 DISCUSSION

Pulmonary hypertension is no longer considered an untreatable disease. As a result it is important that any investigation has high sensitivity and negative predictive value. Measurements of the great vessels have been suggested as an accurate method of detecting and quantifying raised pulmonary artery pressure (139, 190). This is the first study to compare the accuracy of these measurements with doppler echocardiography, the current gold standard. It is also the first prospective study to show the validity of this technique in the initial assessment of patients with both primary and secondary pulmonary hypertension.

Although this is a small study, we have shown that measurements of the great vessels may detect raised pulmonary artery pressure with better sensitivity, specificity and predictive value than doppler echocardiography. A larger study will be necessary to confirm these findings. We have also demonstrated that it may be possible to make estimates of mean pulmonary artery pressure with greater accuracy with this technique. This may be because doppler echocardiography is operator dependant and can be influenced by short-term physiological variables such as heart rate, posture, hydration status and supplementary oxygen (all of which also affect the real-time measurements made at right heart catheterisation) (52). Anatomical measurements of the great vessels are therefore likely to be more reproducible and may provide a more clinically relevant assessment of disease progression or response to treatment. Furthermore, although doppler echocardiography was successfully performed in almost all of the patients in this study, there is a failure rate of up to 60% in some patient groups due to body habitus, undetectable tricuspid regurgitation or co-existing lung disease (78). In comparison MRI scans were generally well tolerated with adequate images obtained in a few minutes.

Our data are similar to those reported in earlier studies, and show similar correlations (Table 6C). Although most previous investigators did not use the currently accepted definition of pulmonary hypertension (mean PAP > 25 mmHg), our data can still be compared with all except Kuriyama et al (140), since none of our normal subjects had a mean PAP of between 20 and 25 mmHg. We found a higher sensitivity and lower specificity for MPAD/AOD than that reported by Ng et al (139).

Table 6C: Studies reporting correlations between measurements of the great vessels and pulmonary artery pressure

Studies	Measurement	Upper limit of normal	Sensitivity	Specificity	r values
Kuriyama et al (n = 32)*	MPAD	28.6mm	69%	100%	0.83
	MPAD/BSA				0.81
Bouchard et al	MPAD				0.76
(n=17)***	MPAD/AOD				0.59
Murray et al (n = 12)***	MPAD				None
	MPAD/AOD				0.7
Haimovici et al (n = 55)*	MPAD				0.67
	MPAD/BSA				0.66
Tan et al (n = 45)**	MPAD	29 mm	87%	89%	None
Edwards et al (n = 12)**	MPAD	33.2 mm	58%	95%	
Ng et al (n = 50)**	MPAD	30 mm	68%	100%	0.74
	MPAD/AOD	1.0	70%	92%	0.74
This study***	MPAD	33.2mm	79%	100%	0.62
	MPAD/BSA	16	89%	86%	0.72
	MPAD/AOD	1.0	95%	57%	0.82

FOOTNOTES:

* = Pulmonary hypertension defined as mean PAP > 18 mmHg, ** = Pulmonary hypertension defined as mean PAP > 20 mmHg, *** = Pulmonary hypertension defined as mean PAP > 25 mmHg, MPAD = Main pulmonary artery diameter, BSA = Body surface area, AOD = Diameter of descending aorta

This suggests that a ratio somewhat higher than the 1.0 proposed may be a better test for the presence of raised pulmonary artery pressure. An alternative explanation would be that our subjects differed from theirs; their study was retrospective and 32 out of 50 subjects had undergone investigation as part of a transplant assessment, whereas ours was prospective and unselected. There have been two other prospective studies however neither were unselected; Murray et al studied 12 adults and children with primary pulmonary hypertension (124) and Haimovici et al reported on a group of patients referred for a transplant assessment (141).

There are a number of weaknesses in our study. No attempt was made to blind the reporting of scans which may have led to bias. Four of our subjects (16,17,20,21)

received oxygen during cardiac catheterisation and echocardiography but not during MRI. Although this could conceivably have affected the results, it would have been expected to weaken and not strengthen our findings. MRI measurements were not made at the same point in the cardiac cycle and vascular girth is likely to vary with the degree of blood flow, however once again this would have been expected to reduce accuracy and weaken our results. Our values for main pulmonary artery diameter are also similar to those reported in previous studies (124, 189). The main pulmonary artery is short, and it is possible that images were not taken at the point of maximum diameter, but this error would also apply to subjects without pulmonary hypertension, and should also reduce the discriminatory accuracy of the technique.

In summary, this prospective study has shown that a main pulmonary artery diameter of > 33.2 mm and a ratio of mean pulmonary artery diameter over aortic diameter of > 1.0 can be used to detect raised pulmonary artery pressure with better sensitivity and specificity than doppler echocardiography. The ratio of main pulmonary artery diameter over aortic diameter also correlated more closely with mean pulmonary artery pressure than doppler echocardiography in patients with both primary and secondary pulmonary hypertension.

7 Flow in right pulmonary artery

7.1 Introduction

One of the first investigators to consider flow was Leonardo da Vinci (1452 – 1519). He proposed that a suspension of particles in a glass container could be used to study internal currents (191), and this approach is still used in modern fluid mechanics. Blood flow is a more complex process governed by several factors, including cardiac function, vascular anatomy and compliance, blood viscosity and the presence of endothelial disease. MRI has provided a versatile new clinical tool for studying blood flow non-invasively and several different techniques have been described in the past few years. These methods utilise one of the following MR effects: phase shift, 3D-Fourier encoding, time of flight and in-flow/out-flow. Phase shift velocity mapping, first proposed by Moran in 1982 (192), is the most extensively validated technique in the clinical setting due to its accuracy and easy applicability and was used in this study (193).

The principle of phase shift velocity mapping is that the MR signal of a moving target (i.e: blood) in a magnetic field changes in proportion to its velocity and direction of travel (phase shift). The confounding effect of a non-moving target (i.e: tissue) is eliminated by reversing the gradient of the magnetic field for the same period of time which has the effect of cancelling out the MR signal produced by all motionless targets. The phase image is further "cleaned" by acquiring two phase images, one with and one without velocity mapping. Subtracting one from the other leaves only the velocity-related phase shifts (193).

The use of MR phase shift velocity mapping to measure flow has been validated in phantom and animal studies (156, 158, 159). Human studies have shown good agreement with doppler echocardiography for normal aortic blood flow (160), peak jet velocity in patients with valve disease (157) and stroke volume and cardiac output (161). Measurements of blood flow in the pulmonary artery and aorta show close agreement with left ventricular stroke volume calculated as described earlier (Chapter 4) in normal subjects (162, 163).

MRI has several advantages over doppler echocardiography. It can measure flow velocity in any direction irrespective of the imaging plane. It also allows the simultaneous measurement of vessel cross-sectional area and mean flow velocity, allowing the calculation of volume flow and therefore stroke volume and cardiac output (193). Its versatility makes it ideally suited for studying the complex flow patterns in the heart and great vessels, and accurate anatomical information can be simultaneously provided for the surgeon. In 10 to 25% of cases the main pulmonary artery cannot be imaged using doppler echocardiography, and misalignment of the doppler signal results in underestimation of flow velocity (194). However, like doppler echocardiography, MR can only estimate pressure indirectly, and interventions such as vasodilator studies or exercise studies are, at present, more easily and safely done in the cardiac catheter laboratory.

Significant differences in flow velocities and flow time curves have been shown in the pulmonary arteries between normal subjects and patients with pulmonary hypertension, using both MRI and doppler echocardiography. Increased retrograde pulmonary flow, mid-systolic notching, reduced pulmonary artery distensibility, a slower and more irregular flow velocity profile and a decreased acceleration time (AT) and acceleration time over ejection time ratio (AT/ET) are recognised markers of raised pulmonary artery pressure (79, 82, 126, 127, 162, 171, 195, 196).

We wondered whether simple measurements made using MR flow quantification would provide a clinically useful non-invasive method of detecting and quantifying pulmonary hypertension. We therefore used MRI to measure mean velocity (MV), peak velocity (PV), AT and AT/ET in the right pulmonary artery in patients undergoing cardiac catheterisation to investigate suspected pulmonary vascular disease.

7.2 Method

Subjects were recruited as outlined in Chapter 2 and are listed in Table 7A. Flow quantification was performed at the end of the scanning protocol described earlier (section 2.4.1) and broadly followed the method used by Marcus et al (118). An oblique coronal image was obtained through the long axis of the right pulmonary artery (Figure 7A), using a transverse scout image on which the ascending aorta and right pulmonary artery were both visible. An oblique sagittal image was then obtained showing a cross-section of the right pulmonary artery (Figure 7B). This was used to generate a "flow" image on which the circumference of the artery was manually outlined (Figure 7C) and a flow quantification performed. The software then plotted a graph of blood flow velocity on the y-axis against time on the x-axis using the R wave at time 0 to indicate the start of the cardiac cycle (Figure 7D). MV was calculated by the software and PV was defined as the maximum velocity shown by the flow curve, both expressed in centimetres per second (cm/s). The graph was then used to calculate AT and ET as shown (Figure 7D): AT was defined as the time between the onset of systolic blood flow and PV, and ET was defined as the time between the onset of flow and the crossing of the x-axis by the descending flow curve, both expressed in milliseconds (ms) (118).

The MR settings were as follows: A two dimensional gradient-echo pulse sequence was used with excitation angle = 25 ^{o}, TE = 6.5 msec, and receiver bandwidth = 195 Hz. Velocity sensitivity was set at 150 cm/s to avoid aliasing. Measurements were obtained without a breath-hold. The R-R interval time was recorded by simultaneous ECG monitoring.

Table 7A: Patient demographics and MRI flow quantification data

	Sex	Age (yrs)	BSA (m2)	Diagnosis	MPAP mmHg	CO L/min	PVR mmHg .min/L	MV cm/s	PV cm/s	AT ms	AT/ ET
1	F	40	2.01	PPH$^{\alpha}$	52	3.4	*	3.7	23.6	88	0.31
2	M	42	1.67	PPH	63	3.3	14.8	5.0	35.9	62	0.24
3	M	51	1.68	CTD	40	3.5	9.1	9.6	30.2	76	0.23
4	F	53	1.61	No PAHT	16	5.7	0.9	20.1	59.1	144	0.38
5	F	56	1.51	PPH	61	3.7	14.6	10.3	37.5	70	0.25
6	F	32	1.61	No PAHT	19	5.1	2.2	F	F	F	F
7	F	50	1.98	CTEPHT	27	3.9	4.6	c	c	c	c
8	F	38	1.40	CHD	78	5.5	13.5	0.1	46.7	54	0.26
9	M	29	2.00	PP	36	6.7	4.2	F	F	F	F
10	F	44	1.77	CHD	66	4.7	*	5.7	21.8	100	0.50
11	F	54	1.72	No PAHT	15	6.0	1.3	18.6	62.5	91	0.25
12	F	42	1.51	No PAHT	19	4.1	2.2	19.5	54.7	167	0.44
13	F	58	1.82	PPH$^{\alpha}$	31	4.6	4.1	9.5	30.5	104	0.32
14	F	64	1.47	No PAHT$^{\beta}$	16	4.4	2.3	10.9	39.2	74	0.26
15	F	33	1.63	CHD	78	6.2	11.1	4.3	23.5	100	0.34
16	M	58	1.92	CTD$^{\beta\chi}$	44	2.7	*	x	x	x	x
17	F	61	1.40	CTD$^{\chi}$	34	2.8	10.7	6.3	21.5	101	0.29
18	M	62	1.95	PPH$^{\alpha}$	53	3.6	11.1	8.2	18.1	307	0.50
19	M	51	1.86	COPD	29	3.7	4.6	F	F	F	F
20	M	60	2.00	COPD$^{\beta\chi}$	39	4.8	5.2	5.1	14.7	140	0.41
21	M	66	1.83	PPH$^{\chi}$	40	2.6	12.7	4.0	21.7	70	0.25
22	F	31	1.92	PP	41	6.3	4.9	10.2	28.8	140	0.34
23	F	48	1.83	No PAHT	16	3.4	1.5	17.8	51.4	195	0.51
24	F	68	1.75	CTD	35	5.4	4.3	9.7	32.9	85	0.24
25	F	60	1.97	No PAHT	16	6.8	1.3	18.5	45.7	140	0.42
26	F	57	1.59	HHT	53	6.4	7.3	8.5	18.6	85	0.28
27	F	43	1.94	CTD	38	4.6	7.2	5.9	16.5	142	0.36
28	M	59	1.66	PPH	47	3.7	12.2	5.8	15.9	112	0.33

FOOTNOTES:

BSA = Body surface area, MPAP = Mean pulmonary artery pressure, CO = Cardiac output, PVR = Pulmonary vascular resistance, MV = Mean velocity in right pulmonary artery, PV = Peak velocity in right pulmonary artery, AT = Acceleration time, ET = Ejection time, PAHT = Pulmonary arterial hypertension, PPH = Primary pulmonary hypertension, CTD = Connective tissue disease, CTEPHT = Chronic thromboembolic pulmonary hypertension, CHD = Congenital heart disease, PP = Portopulmonary hypertension, HHT = Hereditary haemorrhagic telangiectasia, $^{\alpha}$ = Systemic hypertension, $^{\beta}$ = Ischaemic heart disease, $^{\chi}$ = Long term oxygen therapy, * = Pulmonary artery occlusion pressure unobtainable, F = Not obtainable due to technical failure, x = subject exhaustion, c = Claustrophobia

Figures 7A-7C: MRI flow quantification

Figure 7A

Figure 7B

Right pulmonary artery

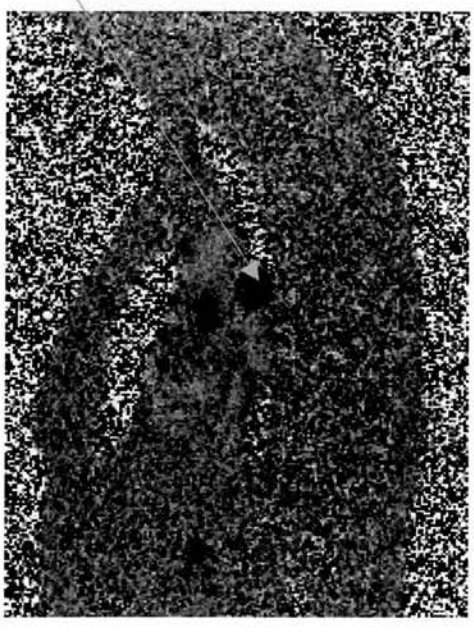
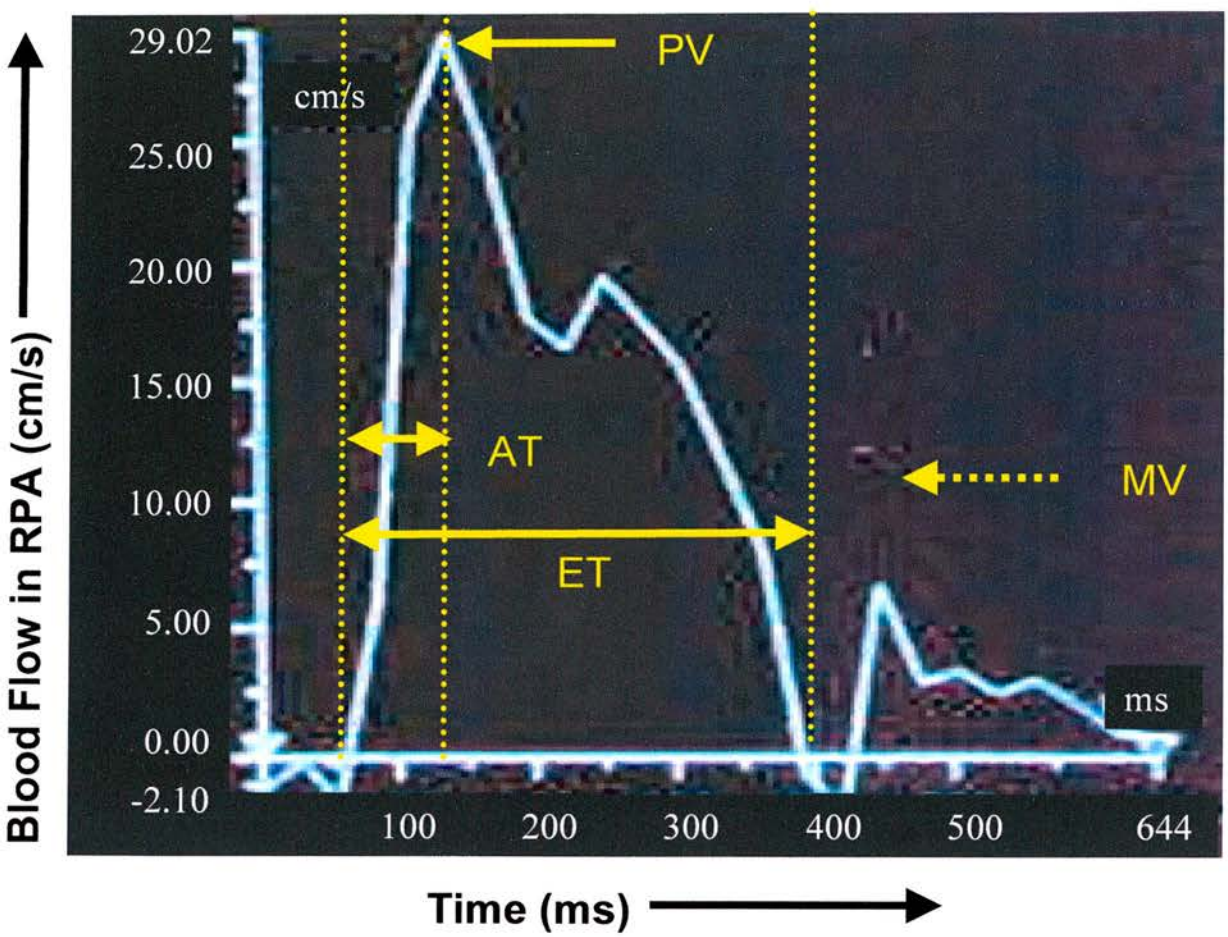


Figure 7C

Figure 7D: Calculation of MV, PV, AT and ET



MV = mean velocity, PV = peak velocity, AT = acceleration time, ET = ejection time, RPA = right pulmonary artery

7.3 Results

Twenty-two out of twenty-eight subjects underwent MRI flow quantification within two days of cardiac catheterisation. A further six were scanned within two weeks (subjects 1,2,6,15,19 and 21). There were no significant changes in symptoms or therapy in the interval between MRI and cardiac catheterisation. Measurements of MV, PV, AT and ET were unsuccessful in five subjects due to acute claustrophobia (subject 7), exhaustion (subject 16) and technical failure (subjects 6, 9 and 19). The data is shown along with patient demographics in Table 7A with statistical analysis of "normal" versus PAHT in Table 7B. Correlations between MRI and cardiac catheter data are shown in Figures 7E-7H and Table 7C with sensitivities, specificities, positive and negative predictive values in Table 7D.

7.3.1 Mean velocity in right pulmonary artery

There was a good negative correlation between MV and both mean PAP ($r = -0.8$, Figure 7E) and PVR ($r = -0.79$, Figure 7G). However it can be seen from Figures 7E and 7G respectively that this is largely a result of five of the six subjects with normal mean PAP behaving as "outliers". When the data was reanalysed after exclusion of subjects with normal PAP a weaker correlation was obtained with mean PAP ($r = -0.51$) and PVR ($r = -0.47$, see Table 7C). The sixth "normal" subject, who had a MV similar to those with raised mean PAP as well as the lowest PV (subject 14), displayed an abnormal rise in PAP with straight leg raising exercise during cardiac catheterisation. If we take a MV $<$ 15 cm/s as indicative of PAHT then sensitivity and specificity were 100% and 83% respectively for those actually scanned, but fell to 81% and 71% when an "intention to scan" analysis was done. Positive and negative predictive values were 94% and 100% respectively (Table 7D).

7.3.2 Peak velocity in right pulmonary artery

There was a weak negative correlation between PV and both mean PAP (r = -0.5, Figure 7F) and PVR (r = -0.52, Figure 7H). The subjects with normal mean PAP were fairly evenly spread however both correlations became weakly positive after they were excluded from the analysis (Table 7C), although this finding did not achieve statistical significance. Taking a PV < 40 cm/s as indicative of PAHT gave a sensitivity and specificity of 94% and 83% respectively, falling to 76% and 71% after an "intention to scan" analysis. Positive and negative predictive values were 94% and 83% respectively (Table 7D).

7.3.3 Acceleration time and AT/ET

There were no significant correlations between AT and AT/ET and mean PAP or PVR. Furthermore, AT and AT/ET did not differ significantly between normal subjects and those with PAHT (Table 7B).

Table 7B: Comparison : Normals vs PAHT

	Normals (n=6)			PAHT (n=17)			p - value
	Mean	±SD	Range	Mean	±SD	Range	
MPAP	16.7	±1.6	15 - 19	47.1	±14.7	27 – 78	0.0000
CO	5.1	±1.2	3.4-6.8	4.3	±1.3	2.6-6.7	0.18
MV	17.6	±3.4	10.9 – 20.1	6.58	±2.8	0.06 – 10.3	0.0002
PV	52.1	±8.6	39.2 – 62.5	25.8	±8.9	14.7 – 46.7	0.0001
AT	135.2	±45.6	74.0 – 195.0	108.0	±57.8	54.0 – 307.0	0.27
AT/ET	0.37	±0.10	0.25 – 0.51	0.32	±0.08	0.23 – 0.50	0.29

FOOTNOTES:

MV = Mean velocity in right pulmonary artery, PV = Peak velocity in right pulmonary artery, AT = Acceleration time, ET = Ejection time, PAHT = Pulmonary arterial hypertension, CO = cardiac output, SD = standard deviation

Table 7C: Correlations (r value) of MV, PV, AT and AT/ET with MPAP and PVR

	MPAP		PVR	
MV	- 0.80	(p<0.001)	- 0.79	(p<0.001)
MV (excluding normals)	- 0.51	(p=0.037)	- 0.47	(p=0.076)
PV	- 0.50	(p=0.016)	- 0.52	(p=0.016)
PV (excluding normals)	0.37	(p=0.147)	0.29	(p=0.302)
AT	- 0.26	(p=0.239)	- 0.27	(p=0.235)
AT/ET	- 0.17	(p=0.506)	- 0.37	(p=0.095)

FOOTNOTES:

MV = Mean velocity in right pulmonary artery, PV = Peak velocity in right pulmonary artery, AT = Acceleration time, ET = Ejection time, MPAP = mean pulmonary artery pressure, PVR = Pulmonary vascular resistance

Table 7D: Sensitivities, specificities, positive and negative predictive values for PAHT using MV and PV

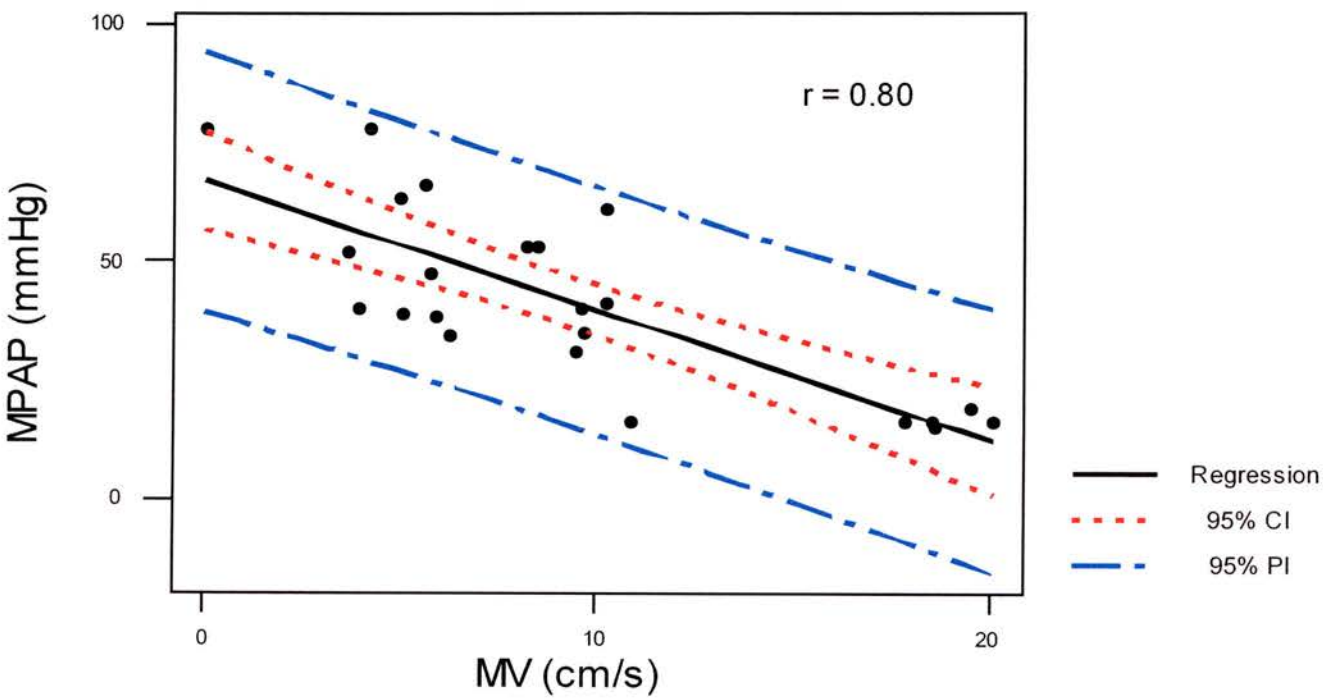
	Sensitivity	Specificity	Positive predictive value	Negative predictive value
MV	100 (17/17)	83 (5/6)	94 (17/18)	100 (5/5)
"Intention to scan"analysis	81 (17/21)	71 (5/7)		
PV	94 (16/17)	83 (5/6)	94 (16/17)	83 (5/6)
"Intention to scan"analysis	76 (16/21)	71 (5/7)		

(Using MV < 15 cm/s, PV < 40 cm/s as indicative of pulmonary arterial hypertension)

FOOTNOTES:

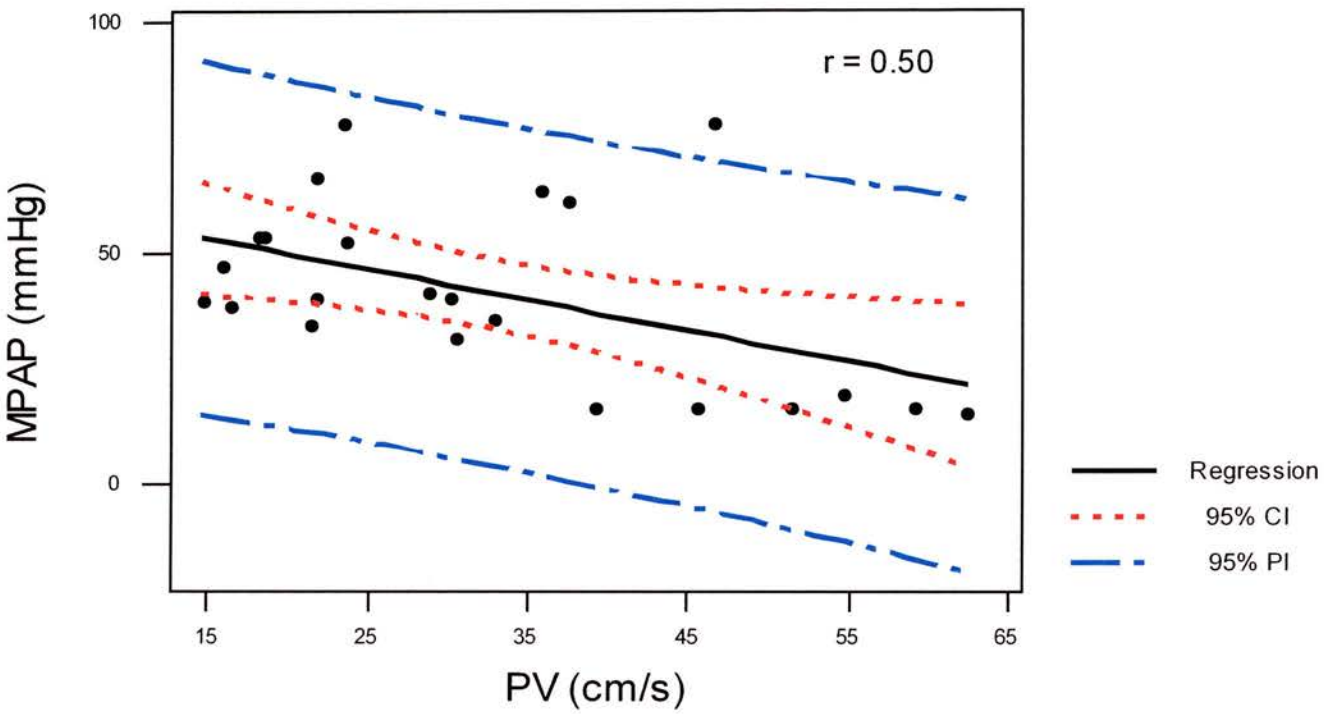
MV = Mean velocity in right pulmonary artery, PV = Peak velocity in right pulmonary artery

Figure 7E: Correlation between MPAP and MV



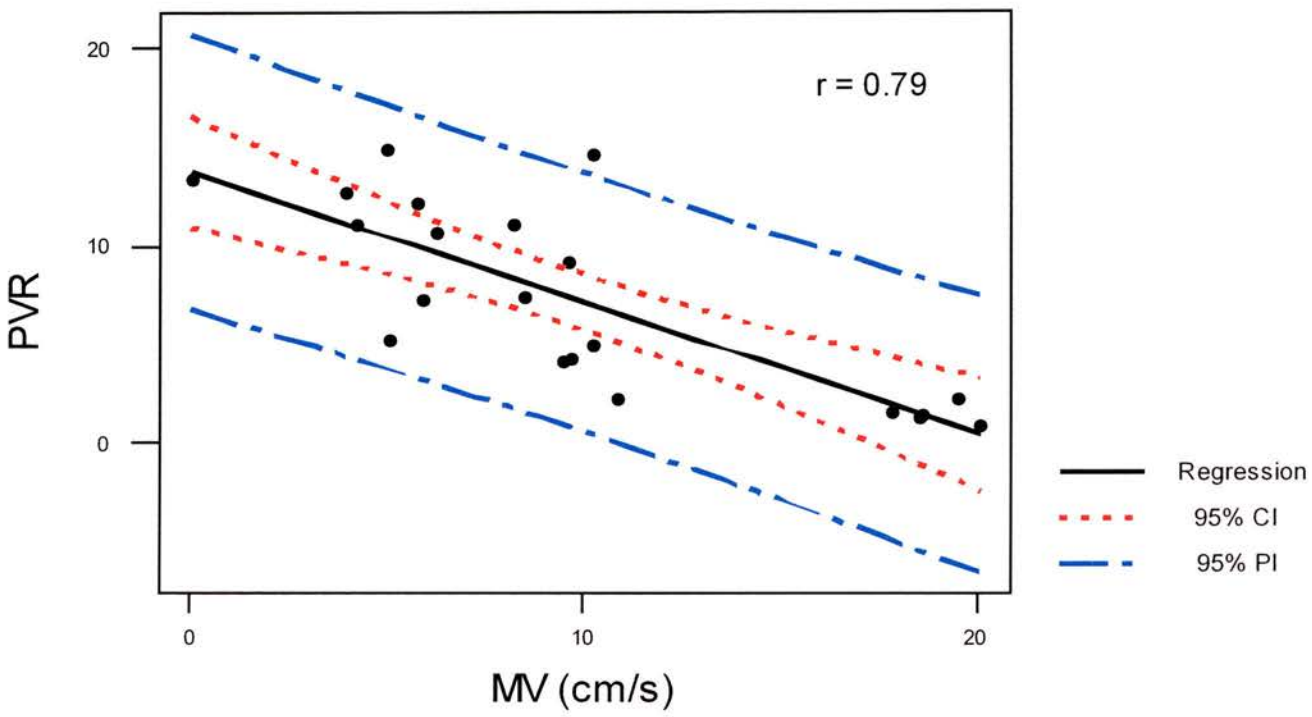
MPAP = mean pulmonary artery pressure, MV = mean velocity,
CI = confidence intervals, PI = prediction intervals

Figure 7F: Correlation between MPAP and PV



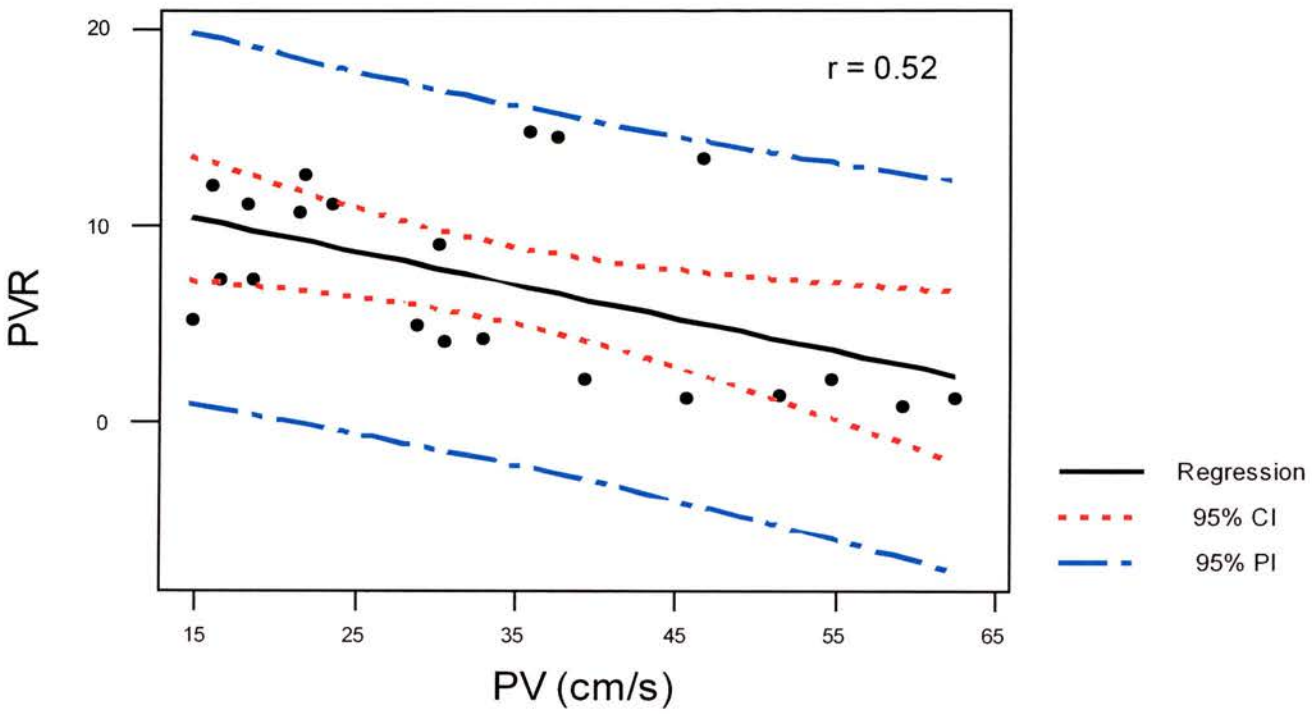
MPAP = mean pulmonary artery pressure, PV = peak velocity,
CI = confidence intervals, PI = prediction intervals

Figure 7G: Correlation between PVR and MV



PVR = pulmonary artery pressure, MV = mean velocity,
CI = confidence intervals, PI = prediction intervals

Figure 7H: Correlation between PVR and PV



MPAP = mean pulmonary artery pressure, PV = peak velocity,
CI = confidence intervals, PI = prediction intervals

7.4 Discussion

This study has shown significant differences in PV and MV in the right pulmonary artery between normal subjects and those with pulmonary hypertension, consistent with the findings of previous studies. Our flow velocity profiles (Figure 7D) show similar phenomena to previous reports, including increased retrograde pulmonary flow and midsystolic notching, that were not seen in the normal population (79, 82, 126, 127, 162, 195). Although there were correlations with mean pulmonary artery pressure and pulmonary vascular resistance for the study group as a whole, these became substantially weaker after those with pulmonary hypertension were analysed separately.

There were no significant correlations between AT and AT/ET and mean pulmonary artery pressure and pulmonary vascular resistance, and more surprisingly, no detectable difference between normal and pulmonary hypertensive subjects. This is inconsistent with the published literature and requires an explanation. The sample size was small and the subjects heterogeneous, and this coupled with the known spontaneous variability of haemodynamic measurements in this disease (108) may provide part of the explanation. Although our pulmonary hypertension subjects had a wide range of mean PAP their cardiac output was relatively well preserved and our values for AT and AT/ET were a little higher than those reported in the literature (79, 127, 196). Furthermore, our "normal subjects" had in fact been referred for investigation because of a strong clinical suspicion of pulmonary vascular disease: subjects 4,11,12 and 25 had abnormal doppler echocardiography and subject 14 with the lowest AT and MV in the "normal" group had an abnormal rise in pulmonary artery pressure during exercise testing in the cardiac catheter laboratory.

Echocardiographic and MRI measurements of blood flow in PAHT correlate well with cardiac output (127) but there have been no reports to our knowledge correlating velocity to mean pulmonary artery pressure or pulmonary vascular resistance. Although we did find significant correlations, in particular for MV, they are not close enough to be clinically useful. This is not surprising as flow is a function of compliance and viscosity as well as pressure and resistance, but there are other possible explanations. Our software calculated an average mean velocity during a cardiac cycle and the average peak velocity

at a particular time point during the cardiac cycle, in common with most commercially available software. This might have been expected to iron out the expected irregularities in flow across the chosen cross-section of right pulmonary artery, but might have had a "dampening" effect on the data, especially if a portion of vessel wall was included when the image was manually outlined. The use of the right pulmonary artery rather than the pulmonary trunk may have contributed to this effect. Although pulmonary artery distensibility is reduced in pulmonary hypertension (162), changes in vessel cross-sectional area relative to the outlined image may have been significant leading to inaccuracy. A more serious source of inaccuracy are the increased retrograde pulmonary systolic flow and mid-systolic notching seen in pulmonary hypertension (79, 126, 162) which are likely to affect MV and PV in an unpredictable way. The right pulmonary artery is not always straight in its course and although care was taken to obtain a true cross-section, an oblique image might inadvertently have been used. Finally, although right and left pulmonary artery blood flow is approximately equal in normal subjects (128), this may not be true in pulmonary hypertension.

The lack of a correlation between AT and AT/ET and mean PAP and pulmonary vascular resistance is less surprising. Although initial echocardiographic studies of AT/ET reported a good correlation with the degree of pulmonary hypertension (79, 80, 83, 197), this was not borne out in later studies (87, 196). Although Tardivon et al reported a good correlation with AT measured by MR, there was no correlation in patients with a mean PAP between 45 and 60 mmHg, and all but three of their patients fell within this range (127). Marcus et al only reported a correlation for AT/ET with systolic PAP in a sample of 11 subjects (171).

In summary, this study has shown that MR measurements of mean and peak blood flow velocity in the right pulmonary artery can be used to detect and quantify pulmonary artery pressure and pulmonary vascular resistance with limited accuracy. MR measurements of AT and AT/ET showed no significant differences between normal subjects and those with pulmonary hypertension.

8 Exercise MRI pilot study

8.1 Introduction

Stress testing is an important part of the assessment of the cardiopulmonary circulation for a number of reasons. It may reveal the presence of diminished reserve or early disease. It may also provide a useful clinical marker of disease severity and response to treatment, and several recent trials of new therapies have used six minute walk testing as a primary endpoint (27, 36). Furthermore, although the predominant symptom experienced by patients with pulmonary hypertension is exercise intolerance, this is not always predicted by resting pulmonary haemodynamics at right heart catheterisation (101), and may relate in part to exercise-induced changes in pulmonary artery blood flow. MRI velocity mapping is an accurate and reliable method of measuring blood flow at rest (see Chapter 7). A number of studies have also reported success in measuring blood flow during or shortly after exercise or pharmacologically induced stress. Significant changes in blood flow have been demonstrated in the tibeal and popliteal arteries after ankle exercise in normal subjects and those with suspected peripheral vascular disease (198, 199). Pennell et al used dobutamine stress testing to evaluate left ventricular function by studying aortic blood flow curves in 25 subjects suspected of having coronary artery disease (200). Mohiaddin et al used a breathhold technique to measure blood flow in the descending thoracic aorta before and after supine exercise using a home made pedaling apparatus (201). MR compatible supine cycle ergometry is now available and has been successfully used to measure blood flow in the aorta and pulmonary artery during exercise in normal volunteers without a breathhold (202), although there have been difficulties with movement artefact and ECG triggering accuracy (203).

To our knowledge, there have been no attempts to study exercise-related changes in pulmonary artery blood flow in patients with pulmonary hypertension using MRI velocity mapping. We therefore undertook this pilot study to see whether MRI flow quantification can be used to study the changes in flow velocity profiles in the right pulmonary artery after exercise.

8.2 Method

All subjects who underwent MRI flow quantification in our previous study were eligible, however because the exercise flow quantification protocol was only instituted at a later date, enrolment only began with subject twenty-one. We initially attempted to perform adequate exercise by means of a pedalling machine designed and built with the help of the department of medical physics, however bedside testing showed that the work load generated in this way was not sufficient to adequately raise heart rate. We therefore decided to use straight leg raising (SLR), modifying the protocol used routinely in our cardiac catheter laboratory. Following acquisition of resting flow measurements as described in the last chapter, subjects were asked to maintain the same position while their bed was moved out of the scanner. After recording the resting heart rate subjects were asked to perform three minutes of SLR exercise by lifting each leg alternately as high as possible while keeping it extended. This was supervised with suitable vocal encouragement. As soon as three minutes of SLR was completed or the subject became exhausted the bed was moved back into the scanner and a further flow quantification performed in the right pulmonary artery, using the same MRI settings as before. The data was then analysed as previously described.

All subjects also underwent cardiac catheterisation and performed a six minute walk test (6mwt).

8.3 Results

8.3.1 General

Eight subjects were enrolled, two with PPH, two with CTD, one with PP, one with HHT and two with normal MPAP at cardiac catheterisation (Table 8A). The interval between cardiac catheterisation, 6mwt and MRI scanning was less than 2 days in all except subjects 27 and 28 where it was four weeks. Exercise MRI flow measurements were only obtained in four subjects, two with PPH (subjects 21 and 28) one PP (subject 22) and one with normal haemodynamics (subject 23) and the results are shown in Table 8B. Three

subjects preferred not to do any exercise at the end of the MRI protocol due to back pain (subjects 26 and 27) or exhaustion (subject 24). Measurements were not possible in subject 25 because the exercise resulted in her being out of position and flow quantification could not be performed.

Table 8A: Patient demographics, diagnoses and MRI flow data at rest

	Sex	Age yrs	Diagnosis	MPAP mmHg	CO L/min	PVR mmHg .min/L	MV cm/s	PV cm/s	AT ms	AT/ ET	6mwt m
21	M	66	PPH$^{\chi}$	40	2.6	12.7	4.0	21.7	70	0.25	210
22	F	31	PP	41	6.3	4.9	10.2	28.8	140	0.34	260
23	F	48	No PAHT	16	3.4	1.5	17.8	51.4	195	0.51	550
24	F	68	CTD	35	5.4	4.3	9.7	32.9	85	0.24	345
25	F	60	No PAHT	16	6.8	1.3	18.5	45.7	140	0.42	360
26	F	57	HHT	53	6.4	7.3	8.5	18.6	85	0.28	350
27	F	43	CTD	38	4.6	7.2	5.9	16.5	142	0.36	263
28	M	59	PPH	47	3.7	12.2	5.8	15.9	112	0.33	438

Table 8B: Exercise MRI Flow Data

	HR (rest)	SLR duration (s)	HR (After SLR)	MV cm/s	PV cm/s	AT ms	AT/ ET	Comments
21	80	180	128	4.5	20.5	91	0.30	
22	70	120	120	10.6	26.0	140	0.36	
23	60	180	80	23.1	66.3	165	0.46	
24	64							No SLR (exhaustion)
25	94	150	125					Out of position after SLR
26	108							No SLR (back pain)
27	67							No SLR (back pain)
28	69	180	87	7.2	22.5	95	0.27	

FOOTNOTES:

MPAP = Mean pulmonary artery pressure, CO = Cardiac output, PVR = Pulmonary vascular resistance, MV = Mean velocity in right pulmonary artery, PV = Peak velocity in right pulmonary artery, AT = Acceleration time, ET = Ejection time, 6mwt = Six minute walk test, PAHT = Pulmonary arterial hypertension, PPH = Primary pulmonary hypertension, CTD = Connective tissue disease, PP = Portopulmonary hypertension, HHT = Hereditary haemorrhagic telangiectasia, $^{\chi}$ = Long term oxygen therapy, SLR = Straight leg raising exercise

8.3.2 MRI flow measurements

There was a significant rise in heart rate (over 25%) following exercise in all four subjects. Although subject 22 did not manage three minutes of SLR, she had the largest rise in heart rate, signifying good effort. In subjects 23 and 28 both MV and PV rose, whereas in subjects 21 and 22 MV rose and PV fell (Figure 8A). This suggests a flattening of the flow velocity profile in subjects 21 and 22 (Figure 8A). Similarly, AT and AT/ET fell in subjects 23 and 28, whereas they rose or remained unchanged in subjects 21 and 22 (Figure 8A).

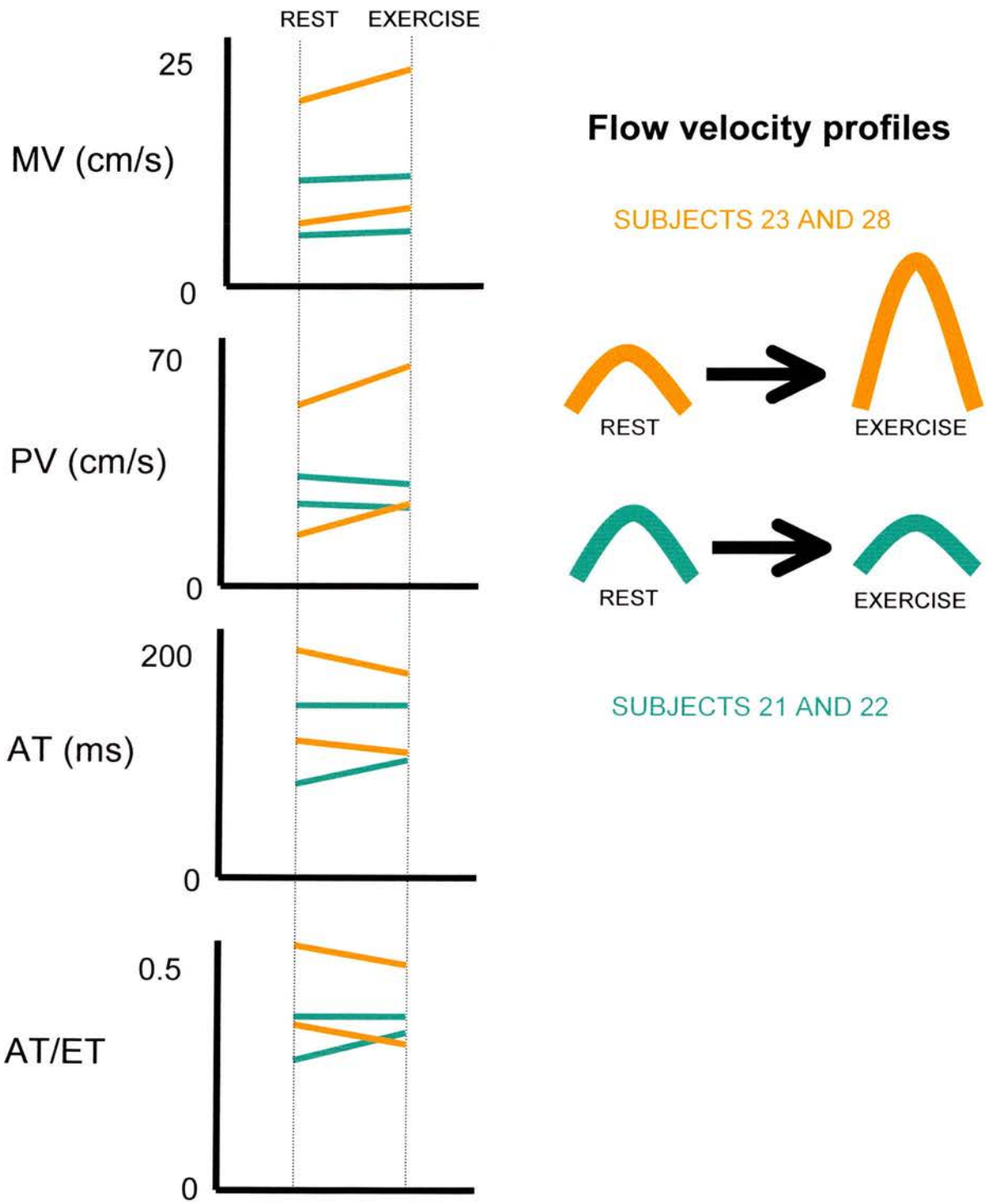
8.3.3 6mwt

Exercise tolerance was relatively well preserved in both subjects 23 and 28, whereas it was poor in subjects 21 and 22 (Table 8A).

8.4 Discussion

This small pilot study suggests that it may be possible to use MRI velocity mapping to assess changes in blood flow in the pulmonary circulation following exercise. It should be emphasised that this is very preliminary data on a small number of subjects and therefore should be interpreted with caution, however taken at face value our results suggest that resting pulmonary haemodynamics may not predict changes in blood flow velocity profiles in this group of patients. As predicted by his good exercise tolerance, subject 28 appeared to have a similar change in flow velocity profile to subject 23 who had normal haemodynamics, in spite of having a similar mean pulmonary artery pressure to subjects 21 and 22. This difference is not explained by resting cardiac output or pulmonary vascular resistance, as can be seen from table 8A. We know that the magnitude of the rise in pulmonary artery pressure with exercise is not predicted by resting haemodynamics (52), and it is plausible that flattening of the flow velocity profile occurs in those patients with a greater rise in pressure. More work needs to be done to validate these findings and assess the feasibility of this approach.

Figure 8A: Exercise-related changes in MV, PV, AT and ET



MV = mean velocity, PV = peak velocity, AT = acceleration time, ET = ejection time

Stress testing is potentially hazardous in patients with pulmonary hypertension. The normal pulmonary circulation is remarkably compliant and can cope with a six-fold rise in cardiac output with minimal change in mean pulmonary artery pressure (102). This compliance is lost in pulmonary vascular disease and pulmonary artery pressure rises rapidly with exercise. The extent of this rise is not predicted by resting pulmonary haemodynamics (52). Left ventricular filling is also impaired due to right ventricular pressure overload (171), and this coupled with rising pulmonary artery pressure eventually results in a reduction in left ventricular filling. This in turn results in falling cardiac output and syncope. A further complication is right ventricular ischaemia caused by the increasing oxygen demand of the hypertrophied right ventricle, and this may provoke potentially fatal arrhythmias. In spite of this, several studies have subjected patients with pulmonary hypertension to symptom-limited exercise testing with few adverse events reported (204), and cardiopulmonary exercise testing has been advocated as a sensitive test for detecting and quantifying pulmonary vascular disease (103), and providing prognostic information (205). There were no adverse events in our study, and although three out of our eight subjects were intolerant of our stress testing protocol, this is unlikely to be a problem with better patient selection.

The cardiopulmonary circulation can be stressed in two ways: the subject can be asked to perform real physical exercise, or stress can be induced pharmacologically using dobutamine, dipyridamole or adenosine (206). Physical exercise has several advantages: it is of direct clinical relevance to the patient, is non-invasive and physiologically accurate, and the subject remains in control of the situation, which can be seen as an added safety feature. Disadvantages, including motion artefacts and ECG-triggering difficulties (203) can be overcome by real-time image acquisition of images, however this was not widely available on commercial scanners at the time of writing. Pharmacological stress testing has been shown to be safe and well tolerated in the assessment of coronary artery disease (206) but there is little data on the safety of this approach in pulmonary vascular disease. Tulevski et al used dobutamine stress MRI to study forty-seven subjects with chronic right ventricular pressure overload due to transposition of the great arteries or a subpulmonic right ventricle. They reported only

one arrhythmic event and three episodes of nausea and vomiting (207), but there have been no other relevant published studies.

In summary, this pilot study has shown that it may be possible to use MRI velocity mapping to measure exercise related changes in pulmonary artery blood flow in pulmonary hypertension. Studying these changes may help in understanding the differences in exercise tolerance between patients with similar resting pulmonary haemodynamics.

9 Conclusions

Magnetic resonance imaging is an exciting and innovative form of imaging with an expanding list of clinical applications. It has the potential to make non-invasive anatomical and physiological measurements reliably and accurately in the vast majority of subjects without recourse to radiation in almost every field of medicine, from cardiology to neurology. It can be used as an alternative to post mortem studies (208) with obvious advantages in children and those with particular religious beliefs. As the technology advances, with ever faster and more compact scanners becoming available, the problems of claustrophobia, noise and limited access are being addressed. Costs are coming down but still limit availability at the time of writing.

Pulmonary hypertension is a rare disease with, until recently, a poor prognosis. The plethora of new therapies that have recently become available have reinforced the need for objective and accurate methods of monitoring disease progression and response to treatment. As discussed in the Introduction, there are good reasons why assessments of pulmonary haemodynamics and exercise capacity alone are likely to be inadequate. MRI can provide a holistic approach to the assessment of the cardiopulmonary circulation. A single examination can provide accurate and reproducible measurements of right ventricular morphology, including mass, wall thickness and chamber volume and also of the great vessels in the cardiopulmonary circulation. These measurements can be used to estimate pulmonary artery pressure with similar or better accuracy than doppler echocardiography, and have the advantage of providing a measure of the recent burden of pulmonary vascular disease without being influenced by transient physiological variables. An analogy may be made with the use of glycosylated haemoglobin instead of blood glucose to assess glycaemic control in diabetics (166). Measurements of resting and exercise blood flow can be made, and can also be used to detect and quantify pulmonary hypertension. Diagnostic information can be simultaneously obtained at the same sitting: MRI can be used to detect congenital heart disease (209-211), chronic thromboembolic disease (212) and is likely to detect pulmonary veno-occlusive disease with similar accuracy to CT.

MRI does have limitations but was well tolerated by almost all our subjects. The problems of noise, claustrophobia and prolonged breath-holding are fast diminishing with advancing technology. The presence of unsecured ferromagnetic material in the body remains a contraindication. Many patients with pulmonary hypertension are treated with continuous intravenous or subcutaneous prostanoids requiring a syringe pump, which would have to remain outside the scanning room, but this has already been overcome in some departments by having syringe drivers built in to the fabric of the scanner. MRI-compatible monitoring equipment such as pulse oximetry and electrocardiography is already commercially available, which may soon allow pharmacological interventions to be made more safely in the scanner. Experience with dobutamine stress testing in ischaemic heart disease has shown it to be safe and practical (206) and there is no reason why acute vasodilator testing could not be done non-invasively using MRI once criteria for defining "responders" and "non-responders" in terms of changes in blood flow rather than pressure and resistance are agreed.

Pulmonary hypertension is a rare disease with a relatively small number of sufferers, and the costs of treatment are high. The recent designation of specialist Pulmonary Vascular Units in the UK means that the care of these patients should now be concentrated at these five centres (213). In this context, the cost and availability of MRI should not be limiting factors. MRI is already being used routinely in the pre and post-operative assessment of patients with chronic thromboembolic pulmonary hypertension and following transplantation (129, 130, 214, 215). It is likely to become the non-invasive investigation of choice for all patients with pulmonary hypertension in the near future, with doppler echocardiography reserved for initial screening where resources are unavailable.

Future work should be concentrated in a number of areas. We need to know how quickly abnormalities of right ventricular morphology evolve in pulmonary hypertension, whether this process can be reversed. MRI provides the best method currently available of monitoring this process, and has already been used to demonstrate remodelling of the right ventricle after single lung transplantation (129, 130, 214). We also need to know whether these anatomical abnormalities have any prognostic significance, as suggested in Chapter 4. MRI also provides a great opportunity to study exercise-induced changes in right ventricular function and blood flow. This may help to explain differences in

exercise tolerance between patients with right ventricular overload, with or without pulmonary hypertension, such as those with chronic obstructive pulmonary disease.

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Appendix 1 Patient information sheet

This Sheet Has Been Approved By The West Ethics Committee
Information Sheet For Patients/Volunteers In Clinical Research Project

Brief Title of Project **Ambulatory Pulmonary Artery Pressure Monitoring in Pulmonary Hypertension : Relationship with Variables Derived from Cardiopulmonary Exercise Testing and Magnetic Resonance Imaging.**

Patient's Summary

We invite you to participate in a trial of measurement of the blood pressure in the lung circulation. We believe that you have raised lung blood pressure which may be the cause of some or all of your breathlessness, and you are due to have a test called "right heart catheterisation" soon to further investigate this. This should already have been explained to you.

This condition is difficult to diagnose and monitor, and we are searching for a safe, non-invasive method that may eventually replace the right heart catheter in the future. There is good evidence that modern exercise testing or magnetic resonance imaging (MRI) may provide this.

We have developed a technique which allows us to measure the lung blood pressure continuously during normal daily activities, including exercise and sleep. This method involves leaving the right heart catheter in place and recording the data on a small portable tape recorder and has been shown to be reliable. The recorder weighs less than 2 pounds and you are free to move about normally with it. The right heart catheter will be positioned in a vein in the right side of the neck and covered with a dressing. It will be left in overnight and removed the following afternoon, when the data will be downloaded onto a computer and analysed. The whole procedure will be supervised by Dr Peacock who has experience of over 50 studies using this method. There have been no additional side effects to date from leaving the catheter in overnight, apart from discomfort in the side of the neck in some people while it is in place, although there is a theoretical risk of infection, blood clots or heart rhythm problems.

While the catheter is in you will have a gentle exercise test on a bicycle during which we will make simple measurements of breathing and heart rhythm. This will be stopped as soon as you become tired. We may ask you to do this twice, with and without oxygen, after resting for at least half an hour.

You will also have an MRI scan to look at the heart and lungs while you do some simple exercises. This involves lying down on a bed in a large metal tube while a magnetic field is used to take pictures of your heart. It has no side effects and involves no radiation, but it can be noisy and claustrophobic.

We plan to compare the results from the exercise test and MRI with those from the catheter to see if they are reliable.

You should not take part if you are pregnant. It should be noted that your participation in this study may not be of direct benefit to you, but could help in the development of treatment for the benefit of future patients. Your stay in hospital may be prolonged by up to one day.

If you do not wish to participate in this study, or wish to withdraw at any time after commencing the trial, your care will in no way be affected.

If you wish to take part in this study, your General Practitioner will be advised of your participation and the clinical management that you will undergo.

If you have any questions please contact: **Dr Tarek Saba at 0141 2116327**
Clinical Research Fellow

WEST ETHICS COMMITTEE

FORM OF CONSENT FOR PATIENTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Title of Project : **Ambulatory Pulmonary Artery Pressure Monitoring in Pulmonary Hypertension : Relationship with Variables Derived from Cardiopulmonary Exercise Testing and Magnetic Resonance Imaging**

By signing this form you give consent to your participation in the project whose title is at the top of this page. You should have been given a complete explanation of the project to your satisfaction and have been given the opportunity to ask questions. You should have been given a copy of the patient information sheet approved by the West Ethics Committee to read and to keep. Even though you have agreed to take part in the research procedures you may withdraw this consent at any time without the need to explain why and without any prejudice to your care.

Consent:

I,.....(PRINT)

of.....

give my consent to the research procedures above, the nature, purpose and possible consequences of which have been described to me

by.....

Patient's signature.....Date.....

Doctor's signature.....

Appendix 2: Anatomical raw data obtained at MRI

	RVM (g)	LVM (g)	VMI	RVEDV (ml)	LVEDV (ml)	RVWT (mm)	LVPWT (mm)	RVWT/ LVPWT	MPAD (mm)	AOD (mm)	MPAD/ AOD
1	173.9	160.9	1.08	132.9	67.8	16	23	0.70	46	23	2.00
2	142.3	158.1	0.90	135.6	70.2	16	17	0.94	32	20	1.60
3	90.9	122.6	0.74	68.8	78.9	13	14	0.93	39	21	1.86
4	72.3	98.0	0.74	95.2	96.5	7	12	0.58	21	24	0.88
5	85.9	80.5	1.07	79.8	51.1	16	16	1.00	30	17	1.76
6	64.2	125.3	0.51	109.2	84.6	6	13	0.46	30	21	1.43
7	c	c	c	c	c	c	c	c	c	c	c
8	130.5	103.2	1.26	57.1	51.3	21	11	1.91	34	18	1.89
9	138.0	187.1	0.74	142.0	F	11	12	0.92	37	21	1.76
10	144.6	105.4	1.37	108.2	64.6	11	18	0.61	38	19	2.00
11	46.5	109.5	0.42	110.1	71.2	7	12	0.58	22	17	1.29
12	71.4	130.8	0.55	104.9	91.6	4	15	0.27	22	23	0.96
13	62.6	92.4	0.68	99.0	83.3	6	10	0.60	27	26	1.04
14	31.3	139.9	0.22	51.6	79.3	6	15	0.40	15	25	0.60
15	94.1	97.3	0.97	77.3	59.8	17	17	1.00	38	16	2.38
16	sob	sob	sob	ND	ND	11	sob	sob	41	31	1.32
17	121.8	128.3	0.95	93.3	63.3	10	13	0.77	34	26	1.31
18	172.2	183.6	0.94	ND	ND	16	sob	sob	34	22	1.55
19	135.7	192.4	0.71	ND	ND	13	17	0.76	34	24	1.42
20	152.9	204.1	0.75	ND	ND	12	13	0.92	36	31	1.16
21	165.2	152.3	1.08	154.3	68.0	16	14	1.14	38	31	1.22
22	91.8	147.7	0.62	108.4	94.3	6	15	0.40	35	21	1.67
23	66.4	128.2	0.52	91.3	78.9	4	8	0.50	24	23	1.04
24	77.2	141.4	0.55	118.1	90.3	8	12	0.67	39	25	1.56
25	107.2	172.7	0.62	121.5	93.2	9	16	0.56	28	29	0.97
26	160.0	205.0	0.78	155.0	80.6	17	17	1.00	44	26	1.69
27	114.0	202.1	0.56	145.4	109.1	9	16	0.56	42	26	1.62
28	143.0	155.0	0.92	117.2	69.5	14	16	0.88	34	24	1.42

FOOTNOTES:

RVM = right ventricular mass, LVM = left ventricular mass, VMI = ventricular mass index, RVEDV = right ventricular end-diastolic volume, LVEDV = left ventricular end-diastolic volume, RVWT = right ventricular wall thickness, LVPWT = left ventricular posterior wall thickness, MPAD = main pulmonary artery diameter, AOD = diameter of descending aorta, c = claustrophobia, F = technical failure, sob = failed due to breathlessness, ND = not done due to failure of ECG gating.